Extrahepatic metastasis of hepatocellular carcinoma to the paravertebral muscle: A case report

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Abstract

Identification of extrahepatic metastases (EHM) of hepatocellular carcinoma (HCC) has been paradoxically increasing due to an increase in the survival of HCC patients. However, metastasis of HCC to the skeletal muscle tissue is extremely rare. We describe a unique case of HCC metastasizing to the paravertebral muscle. A 55-year-old man with a history of hepatitis B cirrhosis underwent partial liver resection with complete removal of HCC. Three months later, a computed tomography (CT) scan showed intrahepatic recurrence. The tumors were treated with yttrium-90 microspheres, transcatheter arterial chemoembolization, and sorafenib. Six months later, a CT scan showed an enhancing lesion of the left paravertebral muscle that on biopsy were consistent with metastatic HCC. The tumor was treated with stereotactic hypo-fractionated image-guided radiation therapy (SHFRT). A follow-up scan 3 mo post-radiotherapy revealed a stable appearance of the paravertebral muscle metastasis. Because of the progression in the intrahepatic tumors, the patient was treated with capecitabine, which was changed to dasatinib 6 mo later. The patient passed away three years after the primary surgical resection. Management of EHM poses an extreme challenge. This is the first case of HCC with EHM to the paravertebral muscle in which stability of disease was achieved using SHFRT. This case highlights the importance of early detection of hepatitis B viral infection and initiation of anti-viral therapy to decrease recurrence of HCC and prevent EHM.

Key words: Hepatocellular carcinoma; Skeletal muscle; Paravertebral muscle; Extrahepatic metastasis; Stereotactic hypo-fractionated image guided radiation therapy;
Hepatitis B virus

Core tip: Extrahepatic metastases (EHM) of hepatocellular carcinoma (HCC) to skeletal muscle are extremely rare. We describe the first case of HCC with EHM to the paravertebral muscle, in which stability of disease was achieved using stereotactic hypo-fractionated image-guided radiation therapy. A literature review revealed the strong relationship between hepatitis B viral infection and EHM. This case highlights the importance of early detection of viral infection and initiation of anti-viral therapy to decrease recurrence of HCC and prevent EHM.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third most common cause of cancer-related death in the world[1-3]. Worldwide incidence is between 250000 and 100000 new cases per year, and it has been rapidly increasing due to the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections[1-3]. In the United States, HCC related to HCV infection has become the fastest rising cause of cancer-related death, and the incidence has trioped during the past two decades. Survival time in patients with HCC has recently increased as a consequence of advanced diagnostic modalities and treatment methods; however, the 5-year survival rate still remains low at approximately 16%-17%[4,5]. Current available treatment methods include surgical resection, radio-frequency ablation, trans-catheter arterial chemoembolization (TACE), yttrium-90 microspheres, liver transplantation, chemotherapy, and radiotherapy[6].

Because of the improvement in survival, extrahepatic metastases (EHM) are becoming more commonly recognized in patients with HCC, with a reported incidence of 15%-17%[6,7]. The most common sites of EHM are lungs, lymph nodes, bones, and adrenal glands; however, HCC can metastasize to the skeletal muscles and subcutaneous tissues, albeit rarely[7]. In this report, we describe a unique case of HCC metastasizing to the paravertebral muscle, which was treated with stereotactic hypo-fractionated image-guided radiation therapy (SHFRT) and achieved disease stability. We report this case along with a review of the recent literature.

CASE REPORT

A 55-year-old male with a history of HBV-associated liver cirrhosis had an incidental right lobe liver mass 6.0 cm in size identified during a routine computed tomography (CT) scan. His serum alpha-fetoprotein (AFP) level was within the normal range. A magnetic resonance imaging (MRI) scan showed a hyper-intense irregular T2 focus, which distorted the contours of the liver. This focus demonstrated moderate enhancement on the initial phase post-Gadolinium images, with a central hypo-intense area. These imaging characteristics were most compatible with focal nodular hyperplasia, and follow-up at the outpatient clinic was advised. However, the patient was non-compliant and did not visit the clinic until three years later. MRI scan at that time showed that the tumor had increased in size to 9.4 cm, and the patient had a mild elevation in AFP level (15.1 ng/mL). His HBV DNA level was 12.7 × 10^6 copies/mL and he had not received any anti-viral therapies. The patient then underwent partial liver resection with complete removal of the tumor. Histopathological examination revealed the tumor to be a moderate-to-poorly differentiated HCC with vascular invasion. According to the Union for International Cancer Control guidelines, the final stage of the tumor was stage II (pT2N0M0). Due to the elevated viral titer, entecavir 1 mg daily was instituted postoperatively.

Three months later, CT scan showed recurrence of the tumor as three foci: 4 mm in size along the resected plane, 7 mm at S4, and 6 mm at S7. The patient’s HBV DNA level was less than 300 copies/mL. The tumors were treated with yttrium-90 microspheres (TheraSphere®, BTG IM, London, United Kingdom). A total dose of 90 Gy was delivered. One year later, he developed multiple enhancing lesions in the liver. He received three sets of TACE with adriamycin, and finally sorafenib (Nexavar®, Bayer HealthCare AG, Leverkusen, Germany) 200 mg twice daily. Six months later, he complained of back pain, and CT scan showed an enhancing lesion 3.7 cm in size in the left paravertebral muscle (Figure 1). A biopsy of the mass showed moderate-to-poorly differentiated HCC, consistent with metastatic HCC (Figure 2). The tumor was treated with four rounds of SHFRT at 10 Gy per fraction with a total dose of 40 Gy. A follow-up scan at 3 mo post-radiotherapy revealed a stable appearance of the paravertebral muscle metastasis. Because of progression of the intrahepatic tumors, the patient was switched to capetitabine (Xeloda®, Roche, Basel, Switzerland) 1500 mg twice daily once a week for 2 wk. He was later enrolled in a clinical trial and started on dasatinib. The patient passed away more than three years after the primary liver resection.

DISCUSSION

Despite significant advances in the treatment of HCC, the prognosis remains poor. Median survival times for
patients with HCC who have EHM are 4.9-7.0 mo. One, three, and five year survival rates are 21.7%-31.0%, 7.0%-7.1%, and 4.0%, respectively\(^9\). Currently, there is no standardized treatment for HCC patients with EHM. Sorafenib is the first systemic agent that has demonstrated a significant improvement in survival time in patients with advanced HCC; however, the modest improvement of 3 mo is far from satisfactory\(^9\). Systemic cytotoxic chemotherapy agents, such as adriamycin, fluorouracil, cisplatin, etc. are considered palliative treatment options for advanced HCC but have low response rates of less than 10%. Recently, there have been some reports on the efficacy of capetcitabine as a second-line treatment following sorafenib\(^{10,11}\). However, these studies are retrospective in nature with low levels of evidence. Other target agents such as regorafenib, c-Met inhibitor, and check point inhibitors are promising, but still under investigation. Dasatinib, an Src family kinase inhibitor, is reported to have effects on human HCC cell lines\(^{12,13}\), however, the results of a recent clinical study showed insufficient response rates\(^{14}\). Due to lack of highly effective systemic chemotherapy for HCC, enrolling in a clinical trial with a new chemotherapeutic agent is the only option for patients with advanced HCC\(^{15,16}\).

Several authors have reported long-term survivors after aggressive surgery for EHM\(^{17,18}\). From the viewpoint of reducing tumor burden, loco-regional therapy may be a reasonable strategy when the target lesions account for a major portion of the total tumor volume. These reports suggest a potential benefit to loco-regional treatment for intra and/or extrahepatic tumor in HCC patients with EHM. Patients with T1/2 primary tumor or less than two EHM were described as good candidates for aggressive local therapy\(^{19,20}\). A retrospective analysis reported that surgical resection of peritoneal or thoraco-abdominal wall implants from HCC in selected patients (limited number of implanted lesions; intrahepatic lesions absent or predicted locally controllable; and the absence of ascites with sufficient hepatic functional reserve) improved long-term survival, with 1, 3 and 5 year overall survival rate of 71%, 44% and 39%, respectively\(^{21}\). On the other hand, the cause of death in HCC patients with extrahepatic metastasis were mostly related to problems as a consequence of intrahepatic tumors, such as liver failure\(^{8,18}\). In our case, SHFRT was selected for local treatment of EHM, in addition to sorafenib as a systemic treatment, since the tumor invaded deeply into the paravertebral muscle and multiple intrahepatic recurrent HCC foci were identified, suggesting a poor prognosis even after the resection. Although the primary purpose for this radiation was for pain control, it was also effective in the control of disease progression. Our case is the first report of EHM treated by a non-surgical method which led to extrahepatic disease stability.

Vascular invasion of HCC has proven to be a strong determinant of EHM. Hematogenous spread to the lungs, lymph nodes, bones, and adrenals are reported to be the most common sites for EHM. Metastasis of HCC to muscle tissue is an infrequent phenomenon. Skeletal muscle and cardiac muscle are classified as striated muscles, which contain sarcomeres that are arranged into highly organized bundles. The infrequency of muscle metastasis seen in HCC may be attributed to the contractility of muscle, the local pH environment, and the presence of tumor suppressors in the muscle tissue\(^{22}\). Over 40 cases of cardiac muscle metastasis of HCC have been reported, whereas only found 17 cases of skeletal muscle metastasis of HCC have been reported (Table 1)\(^{17,23-37}\). All these cases were reported after 2005, two years before sorafenib was approved by the Food and Drug Administration for the treatment of HCC. Skeletal muscle recurrence occurred in various locations throughout the body, the trunk, and the peripheral musculature, with one case of extraocular muscle metastasis\(^{28}\). The majority of patients were male (16/18 cases) and had a history of HBV infection (10/13 cases, excluding 5 cases with unknown etiology). HBV viral load and anti-viral treatment were not recorded except in our case. Most cases underwent surgical resection as a local treatment (9/17 cases, excluding one case with unknown treatment), and some received radiation therapy as palliative therapy.

**Figure 1** Computed tomography of the recurrent tumor. Computed tomography scan showing an enhancing lesion 3.7 cm in size in the left paravertebral musculature.

**Figure 2** Histology of the paravertebral muscle tumor. A biopsy of the mass showed moderate-to-poorly differentiated hepatocellular carcinoma (HCC), consistent with metastatic HCC (hematoxylin and eosin, × 200).
Table 1  Skeletal muscle metastasis of hepatocellular carcinoma

| Ref. | Year | Age/gender | Background | Treatment (primary lesion) | Muscle recurrence site | Recurrence time (mo) | Treatment (metastasis) | Other lesions | Simultaneous systemic treatment |
|------|------|------------|------------|---------------------------|-----------------------|---------------------|------------------------|--------------|--------------------------------|
| This case | 2017 | 55/M | HBV | Resection | Paravertebral muscle | 21 | SHFRT | Multiple intrahepatic HCC | Sorafenib |
| [23] | 2014 | 36/M | Unknown | Chemo-radiotherapy | Chest wall | 0 | Chemo-radiotherapy | Cisplatin/ adriamycin | Chemo-radiotherapy |
| [23] | 2014 | 31/M | HBV | Resection | Chest wall, pectoral muscles | 0 | Cisplatin/ adriamycin | None | None |
| [24] | 2014 | 47/M | Unknown | Resection | Rectus muscle | 13 | Resection | Sorafenib | None |
| [17] | 2013 | 55/M | HBV | Resection | Pectoralis major | 54 | Radiotherapy | None | None |
| [25] | 2013 | 61/M | Alcohol | None | Iliac muscle | 0 | Chemotherapy | None | None |
| [26] | 2012 | 65/M | HBV | RFA | Intercostal muscle | 24 | Resection | None | None |
| [27] | 2012 | 72/M | Alcohol | TACE | Medial pterygoid muscle | 0 | Radiotherapy | Multiple intrahepatic HCC | Sorafenib |
| [28] | 2012 | 44/M | Unknown | Resection | Extrapleural muscle | 17 | Radiotherapy | None | None |
| [29] | 2011 | 70/M | HBV | Resection | Pectoral muscles | 108 | Resection | None | None |
| [30] | 2009 | 82/M | Unknown | Resection | Diaphragm | 30 | Resection | None | Unknown |
| [31] | 2009 | 62/unknown | HBV | TACE | Pectoral muscle | 96 | Resection | None | Unknown |
| [32] | 2008 | 54/M | HBV | Resection | Rectus femoris muscle | 60 | Sorafenib | Multiple pulmonary metastasis | Sorafenib |
| [33] | 2008 | 52/M | HBV | Liver transplant | Chest wall | 60 | Resection | None | None |
| [34] | 2007 | 63/M | Unknown | Resection | Gastrocnemius muscle | 18 | Resection | None | None |
| [35] | 2007 | 53/M | HCV | None | Gluteus maximus muscle | 0 | Resection | None | None |
| [36] | 2006 | 50/M | HBV | Resection | Psoas muscle | 12 | Resection | None | None |
| [37] | 2005 | 39/F | HBV | Resection | Chest wall | 11 | Resection | None | None |

1Months after the primary treatment; 2At the time of muscle recurrence. M: Male; F: Female; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; TACE: Transcatheter chemoembolization; SHFRT: Stereotactic hypofractionated image-guided radiation therapy; HCC: Hepatocellular carcinoma.

In cases with simultaneous recurrence similar to ours, sorafenib or another chemotherapeutic agent was used as systemic therapy[17,23,25,27,32]. However, even with these treatments, prognosis was extremely poor, ranging from a few weeks to 6 mo.

Previous studies have described the importance of controlling viral status to prevent HCC recurrence and improve survival after curative treatment for HBV-related HCC[38,39]. Huang et al[40] reported that preoperative antiviral treatment decreased viral reactivation rate, and pre- plus postoperative antiviral treatment achieved a better 5-year overall survival rate than postoperative antiviral treatment alone by decreasing HBV-related HCC recurrence. On the other hand, only one study described a correlation between HBV status and EHM. Sasaki et al[41] reported that HBV infection was an independent predictor for the occurrence of EHM in patients with large HCC tumors. In addition, the authors posit that HBV infection might promote the establishment of EHM through modulation of the adhesion-de-adhesion balance of HCC cells[40]. In our case, although the patient’s HBV status was well-controlled by entecavir after hepatectomy, the patient did not receive any anti-viral treatment preoperatively despite a high viral load. No previous case reports of muscle recurrence included patient HBV status or antiviral treatments. Although the relationship between HBV infection and skeletal muscle recurrence has not been clarified, we consider controlling HBV viral load through antiviral treatment prior to surgical intervention important due to the high incidence of HBV infection among patients with HCC with EHM recurrence.

We report the first case of HCC with EHM to the paravertebral muscle. Though this is a single case, it raises interest in detecting EHM at an earlier stage and initiating therapy if the patient’s overall health permits.
A study of surgical and non-surgical treatment with systemic vs loco-regional therapy may shed further light on this topic.

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