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【 CASE REPORT 】

Muscular Metastasis of Hepatocellular Carcinoma: Case Report and Literature Review

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Abstract:

There are few case reports of hepatocellular carcinoma (HCC) metastasis to the skeletal muscle. A 78-year-old man developed a mass in the right shoulder. Washout of contrast medium during contrast-enhanced ultrasonography (CEUS) in both the primary HCC and the metastatic site was detected. Several nodules were scattered throughout the liver on an autopsy. In addition, the moderately differentiated HCC had metastasized to the right teres major muscle. Rare muscular metastasis should be considered if a hepatic tumor is moderately or poorly differentiated HCC. Early washout during CEUS is consistent with a pathological diagnosis of moderately or poorly differentiated HCC.

Key words: contrast-enhanced ultrasonography, hepatocellular carcinoma, muscular metastasis, teres major muscle, moderately differentiated

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Introduction

Hepatocellular carcinoma (HCC) is the fifth-most common cancer in men and the seventh-most common in women worldwide. The etiology of HCC includes chronic infection of hepatitis B virus (HBV) or hepatitis C virus (HCV), nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), alcoholic liver disease, autoimmune liver diseases (e.g., autoimmune hepatitis), primary biliary cholangitis, primary sclerosing cholangitis, and congestive liver disease (e.g., Budd-Chiari syndrome), as well as liver diseases of unknown etiology (1).

As HCC progresses, it metastasizes to distant organs. The most frequently detected sites of HCC in Japan are the lungs (31.5%), lymph nodes (19.0%), and bones (16.7%) (2). Cancers develop in complex tissue environments, which they depend on for invasion and metastasis (3). In general, epithelial-to-mesenchymal transition is a very important step for the initiation of primary tumor invasion (3). In HCC, N-glycosylation of CD147, a tumor-associated glycoprotein, is upregulated during TGF-1-induced epithelial-to-mesenchymal transition, which correlates with tumor metastasis (4). Other studies have also clarified the influence of RNA overexpression on cancer progression.

A high expression of long, noncoding RNA HOXD-AS1 was associated with a poor prognosis and high tumor node metastasis stage among HCC patients and was an independent risk factor for the survival (5). Dong et al. reported that knockdown of a small nucleolar RNA host gene inhibited cell proliferation, invasion, and lung metastasis *in vitro* and *in vivo* (6). In addition, knockdown of the CD147 gene in HCC cells significantly decreased the secretion of matrix metalloproteinase and the invasive potential of HCC cells (7). Recent experimental data have shown that a disintegrin and metalloprotease (ADAM) and matrix metalloprotease participate in cancer formation, progression, and me-

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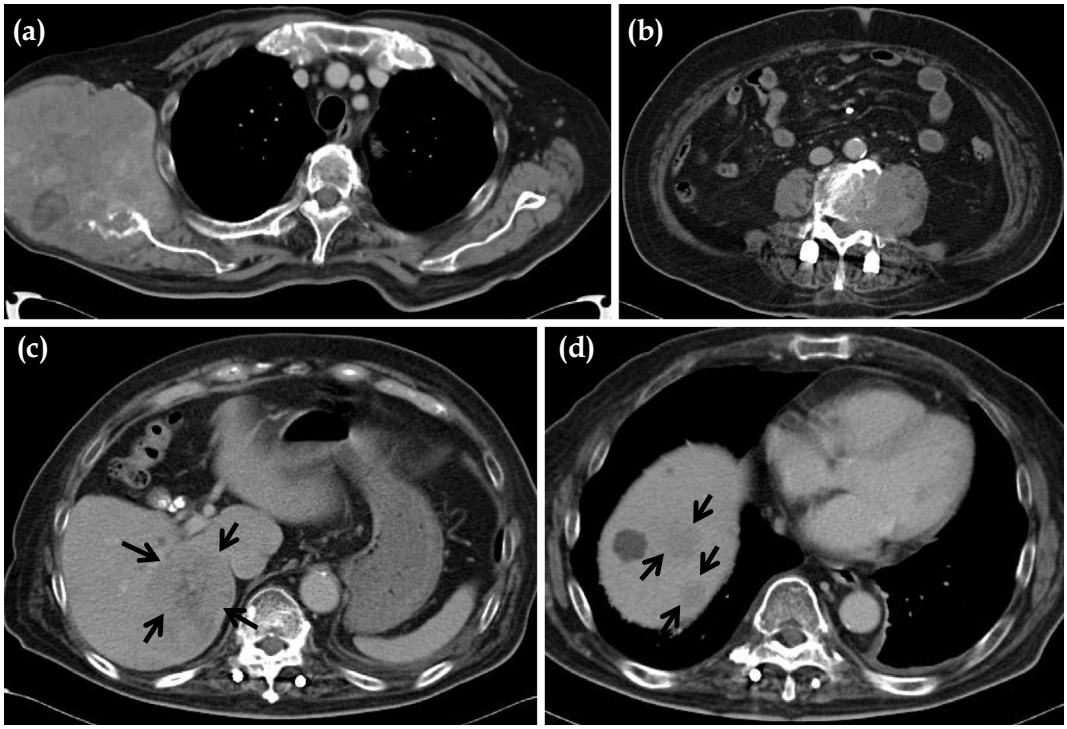

Figure 1. **(a) Contrast-enhanced CT showing the lesion of the right shoulder, (b) the tumor in the para vertebrae portion, and (c, d) multiple intrahepatic hypovascular nodules (arrows).**

tastasis (8).

Recently, the multi-kinase inhibitors, sorafenib and regorafenib have been shown to suppress ADAMs. Furthermore, sorafenib and regorafenib also potentiate immune-mediated hepatoma cell death, enhancing natural killer (NK) cell immunity against tumors by decreasing the expression of ADAMs (9, 10). Importantly, antifungal lomofungin (11), disulfiram (12), leukotriene receptor antagonists (13), and retinoids (14) are also reported as potential drugs enhancing NK cell immunity against human HCC by suppressing the enzymatic power of ADAMs.

In the cancer microenvironment, during the elimination phase for tumor cells, NK cells and T cells work together to destroy developing tumors long before they become clinically apparent (15). However, agents targeting these enzymes have not shown the expected results in most clinical trials, despite their promising activity in many preclinical models (16). Unfortunately, a zymographic analysis of peripheral blood did not show any consistent patterns of change in matrix metalloprotease levels during treatment (17). Efforts to target these enzymes are ongoing, and the pharmacological targeting of cancer by the development of a new generation of effective and selective enzymatic inhibitors is an emerging and promising area of research (16).

Metastasis to the skeletal muscle is rare, accounting for less than 1% of HCCs (18). Of note, the muscle contains proteases and other inhibitors that suppress tumor invasion and growth (19).

We herein report a rare case of HCC with muscular metastasis and describe the clinical features of muscular metastasis in HCC.

Case Report

A 78-year-old Japanese man with hypertension and diabetes mellitus controlled by medication who was a total abstainer developed a lumbar compression fracture and had undergone posterior lumbar spinal fusion in 2014. During regular follow-up by an orthopedic surgeon at the outpatient clinic, he complained of a mass at his right shoulder, back pain, and sensory disorder in the lower legs in 2018. He had noticed the mass at his right shoulder four months ago and felt back pain and sensory disorder for the past month. Contrast-enhanced computed tomography (CT) detected a nodule 140 mm in diameter at the right shoulder (Fig. 1a), lesions adjacent to the lumbar vertebrae (Fig. 1b), and multiple hepatic hypovascular nodules (Fig. 1c, d). The corresponding unenhanced CT findings are shown in Supplementary material 1a-d. There were no apparent lung metastases (Supplementary material 1e-h).

He was referred to us for an examination of the hepatic nodules. A physical examination revealed a painless mass at the right shoulder. The results of the physical examination are shown in Supplementary material 2. His HbA1c level was 5.6% (Supplementary material 3). A blood examination indicated anemia, hypoproteinemia, and elevated levels of liver and biliary enzymes, including gamma-glutamyltranspeptidase. C-reactive protein (CRP) levels were also slightly elevated. The serum levels of α-fetoprotein and protein induced by vitamin K deficiency or antagonists-II were high, whereas those of carcinoembryonic antigen and carbohydrate antigen 19-9 were normal. HBV surface anti-

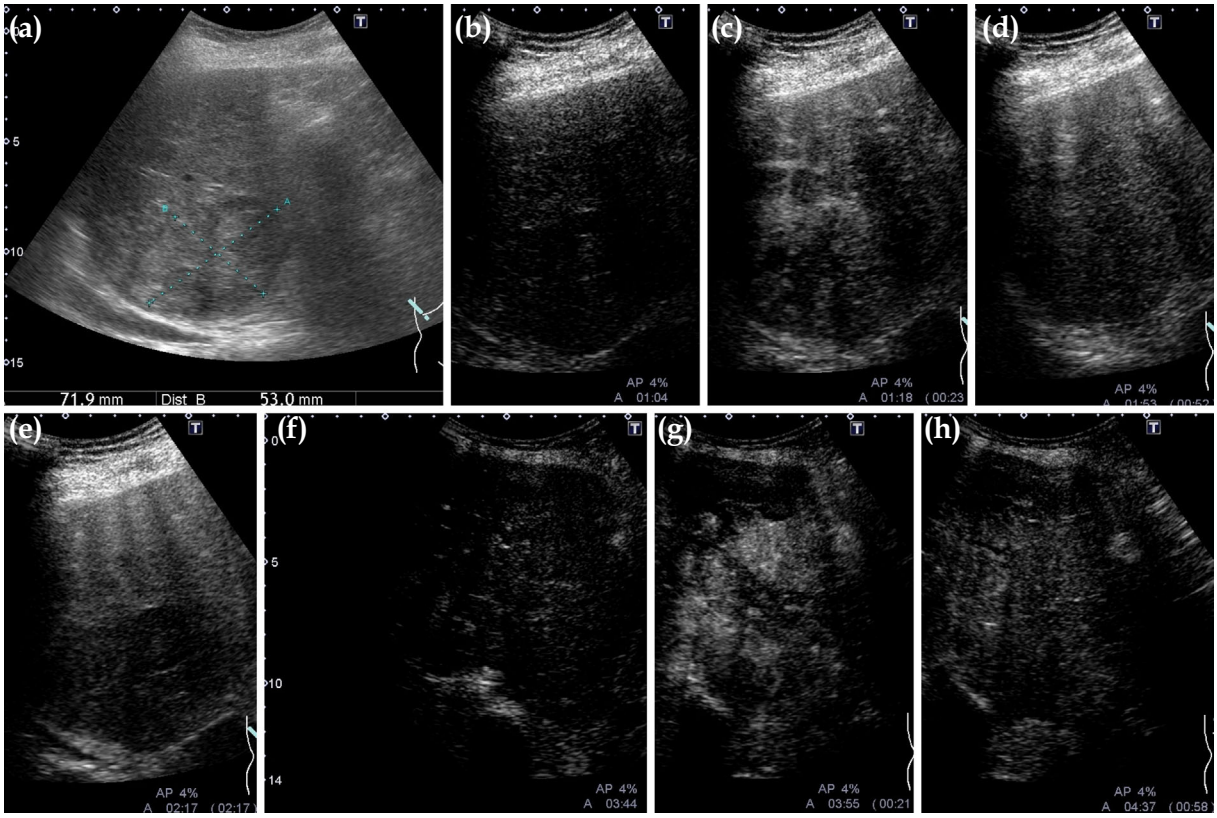

Figure 2. **(a) On conventional abdominal US, there were multiple liver nodules. (b) In the CEUS mode without injection and (c) in the early vascular phase after Sonazoid® was injected, the liver nodules were enhanced uniformly. The enhancement inside the nodules did not persist (d) in the PVLP, and (e) the nodules exhibited washout. The lesion in the right shoulder was also evaluated. A comparison to (f) the figure before reinjection, the findings of vascular pattern, (g) in the early vascular phase and (h) in the PVLP were same as those seen in liver tumors shown above.**

gen and anti-HCV antibody were negative (Supplementary material 3).

Conventional abdominal ultrasonography revealed hepatic nodules (Fig. 2a). Contrast-enhanced ultrasonography (CEUS) was also performed on the sixth day. Sonazoid® is a second-generation microbubble contrast medium used in CEUS to visualize the vascular pattern inside liver nodules (20-22). A bolus of Sonazoid suspension was intravenously injected, and the vascular phase was defined as previously reported (23). In brief, the phases from 15 to 30 seconds and from 30 seconds to 2 minutes after injection were defined as the early vascular phase and the portal venous and late phases (PVLP), respectively (24). Compared to the pre-contrast phase (Fig. 2b), in the early vascular phase, the hepatic nodules were enhanced uniformly (Fig. 2c). The enhancement inside the nodules did not persist in the PVLP, and the nodules disappeared (Fig. 2d, e). Finally, in the post-vascular phase, which was 10 minutes after injection, the tumors exhibited washout (Supplementary material 1i). Furthermore, CEUS indicated a 140-mm lesion in the right shoulder. Compared to the pre-contrast scan (Fig. 2f), the patterns of enhancement in the shoulder lesion in the early vascular phase (Fig. 2g) and in the PVLP (Fig. 2h) were similar to those of the hepatic tumor (Fig. 2c, d). He was admitted to undergo a percutaneous liver needle biopsy on the eighth day, and the hepatic tumor was finally diagnosed as moderately differentiated HCC (Supplementary material 4).

His performance status was 2, and we proposed systemic chemotherapy with a multi-kinase inhibitor in accordance with the desires of the patient and his family. However, the laboratory data worsened, indicating elevated hepatic and biliary enzyme levels and increased values of inflammatory biomarkers, such as the white blood cell count and CRP level, and uric acid (Supplementary material 5). The patient presented with newly initiated pain in the bilateral legs and worsening sensory discomfort. Plain lumbar magnetic resonance imaging (MRI) T2-weighted imaging revealed multiple high-intensity lesions, indicating metastases to lumbar vertebrae L2 and L4 (Supplementary material 6) on the 11th day. On the same day, a technetium-99m bone scan showed areas with an intense radiopharmaceutical uptake in the lumbar vertebrae consistent with the locations detected on MRI and the lesion in the right shoulder (Supplementary material 6). On the 14th day, radiotherapy to the metastatic lumbar vertebrae and oral analgesia were initiated as palliative care. Unfortunately, his systemic condition did not recover, and he died on the 19th day.

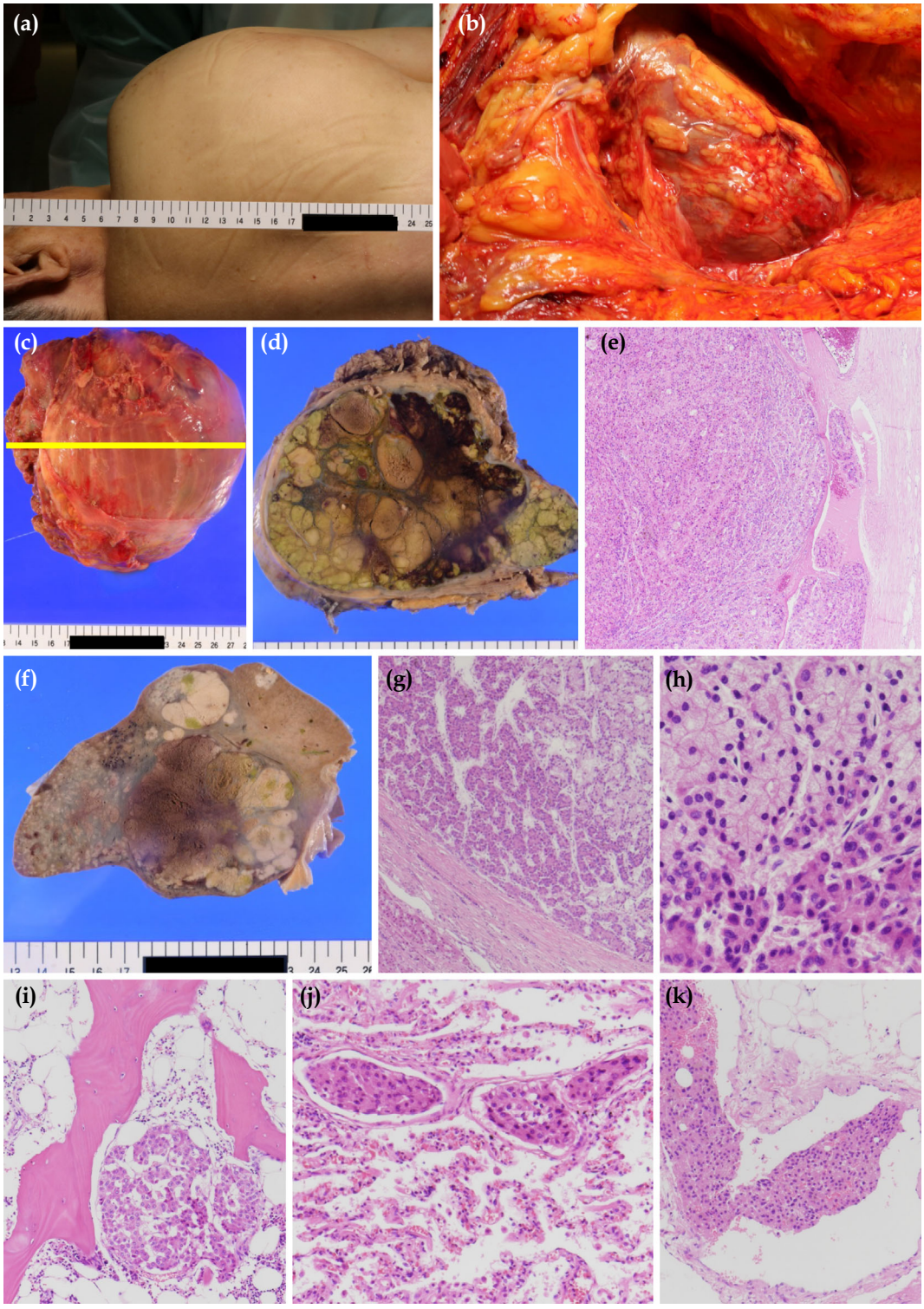

Figure 3. **The findings of the pathologic autopsy are shown. (a, b) The mass at his right shoulder was shown from the dorsal side of the patient. (c-e) It turned out to be metastasis to the right teres major muscle [e; objective, ×20 with Hematoxylin and Eosin (H&E) staining]. The specimens of the hepatic nodules and distant organs were defined as (f-h) primary moderately differentiated HCC with clear cell type and metastatic cancers in the (i) vertebrae and (j) venous metastases to the bilateral lungs and (k) adrenal glands (g: objective, ×20, h: objective, ×100, i-k: objective, ×40 with H&E staining).**

A pathologic autopsy was performed after obtaining written informed consent from the patient's family. The mass at the right shoulder was identified as metastasis to the right teres major muscle (Fig. 3a-e). The final diagnosis was primary moderately differentiated HCC, clear cell type (Fig. 3f-h) with metastasis to the right teres major muscle

and vertebrae (Fig. 3i) and venous metastases to the bilateral lungs (Fig. 3j) and adrenal glands (Fig. 3k). A pathology specimen showed cytoplasmic clearing in some areas, indicative of so-called clear cell tumors (Fig. 3g, h). All the metastatic sites were composed of moderately differentiated HCC cells (Fig. 3e, i-k). The specimen of the hepatic nodules and metastasis to the right teres major muscle were immunohistochemically negative for alpha-fetoprotein (AFP) and positive for hepatocyte specific antigen (Supplementary material 7). In addition, the hepatic specimen without cancer cells was not cirrhotic, and no inflammatory changes with NASH were noted (Supplementary material 8).

Written informed consent was obtained from the patient's family for the publication of this case report and any accompanying images.

Discussion

In the present study, we diagnosed the first case of moderately differentiated HCC with metastasis to the right teres major muscle. Washout of contrast medium during CEUS in both the primary HCC and the metastatic site in the right teres major muscle was detected in the 1-minute phase after injecting contrast medium, which is consistent with a pathological diagnosis of moderately or poorly differentiated HCC rather than well-differentiated HCC.

The most frequent sites of HCC metastasis are the lungs (31.5%), lymph nodes (19.0%), and bones (16.7%) (2). There has been no detailed description of metastasis to the skeletal muscle, and the frequency is considered to be very low. In general, hematogenous metastasis of cancer to the skeletal muscle is extremely rare, accounting for less than 1% of hematogenous metastasis from solid tumors. The most common primary cancers that metastasize to the skeletal muscle are tumors of the lungs (35%), gastrointestinal tract (23%), and kidneys (19%) (17, 23).

There are three major reasons for the low incidence of metastasis to skeletal muscle (18, 19, 24, 25). First, in contrast to the environment in the lungs, liver, and bones, the blood flow to the skeletal muscle is not constant due to muscle contractions, which is not suitable for tumor cell circulation. Second, lactic acid produced by the skeletal muscle suppresses tumor cell growth. Finally, the muscle contains proteases and other inhibitors that suppress tumor invasion and growth. Because this patient had no history of percutaneous procedures in the right shoulder, we believe that the HCC hematogenously metastasized to the right teres major muscle. Because of the very low incidence of muscular metastasis, there have been no previous reports of HCC metastasis to the teres major muscle, and to our knowledge, there has been only one report of metastasis to the teres major muscle for any cancer, which occurred in a patient with colorectal carcinoma (26).

Clear cell HCC in non-cirrhotic liver or liver without hepatitis is rarely reported (27, 28). Therefore, when a hepatic tumor with clear cell features in a patient with an otherwise unremarkable liver background is encountered, metastasis from another primary tumor with clear cell components needs to be excluded (29). In this case, the pathological autopsy indicated no other clear cell carcinomas, such as clear cell carcinoma from the ovaries or clear cell renal cell carcinoma, that could have been the primary lesion. Clear cell HCC is a well-differentiated variant of HCC (29). Previous studies have indicated that clear cell HCC had a better prognosis than conventional HCC (30, 31). This is consistent with our case, wherein all of the pathologic specimens of metastatic sites were diagnosed as moderately differentiated HCC without clear cell type tumors, unlike the primary HCC (Fig. 3e, g-k).

We used CEUS to examine both the primary HCC and the metastatic shoulder nodule. Takahashi et al. (32) focused on the timing of washout during contrast enhancement in 77 histologically proven HCC nodules. Washout was more frequent in poorly differentiated HCC than in moderately differentiated HCC ($p=0.0117$) and well-differentiated HCC ($p=0.0003$) in the 1-minute phase and was more frequent in moderately differentiated HCC than in well-differentiated HCC in the 5-minute ($p=0.0026$) and 10-minute ($p=0.0117$) phases, suggesting that the washout timing can predict cellular differentiation. In this case, washout of contrast medium in both the primary HCC and the metastatic site in the right teres major muscle was detected in the 1-minute phase. This was consistent with the pathological diagnosis of moderately differentiated HCC.

Eighteen cases of HCC with metastasis to the skeletal muscle have been reported in the English literature (Table). Takahashi et al. also reviewed these cases, all of which were reported after 2005 (33). All 18 patients (33-48) were men, and the sites of metastasis were the erector spinae muscles (33), spinal iliopsoas (34, 42, 46), rectus femoris (35), extraocular muscles (39), biceps femoris (47), and quadriceps (48). Eight cases, including our own, provided histological details, and the majority of cases were moderately differentiated HCC (7/8 cases) (33, 37, 39, 40, 44, 48). Only one case was well-differentiated HCC (36). To our knowledge, why men predominate HCC cases with metastasis to the skeletal muscle is unclear. Furthermore, there was a discrepancy between the immunohistochemical findings for AFP and the serum AFP levels. Since the pathological autopsy indicated no other carcinomas that might produce AFP, the reason for this phenomenon is unclear.

The prognosis of HCC patients with multiple distant metastases, including muscular metastases, is poor even with chemotherapy, such as sorafenib, but if intrahepatic control is good, a favorable prognosis can be obtained by aggressive surgical resection.

In our case, surgical resection may have resulted in a better prognosis if the tumor had been detected earlier. However, there are few treatment options for muscular metastasis, and the further accumulation of cases is needed. In our literature search, most cases of muscle metastases of HCC (12 of 18 cases) were detected after surgery for HCC. The

Table. Clinical Cases of HCC with Metastasis to Skeletal Muscle.

Reference	Year	Age	Gender	Background	Locus of muscular metastasis	Size, number (muscular masses)	Recurrence time (mo)	Pathology of muscular metastasis	Treatment for metastasis
(33)	2006	50	Male	HBV	Psoas muscle	5.5×5×4.5 cm, single	12	Unknown	Surgical resection
(34)	2008	54	Male	HBV	Rectus femoris muscle	Unknown, single	60	Unknown	Chemotherapy (sorafenib)
(35)	2009	61	Male	HBV	Pectineal muscle of the right thigh	Unknown, single	96	Well differentiated	Unknown
(36)	2009	82	Male	Unknown	Diaphragm	1.5 cm, single	30	Moderately differentiated	Surgical resection
(37)	2011	70	Male	HBV	The right humerus muscle	5.5 cm, single	108	Unknown	Surgical resection
(38)	2012	44	Male	Unknown	Bilateral multiple extraocular muscle	Unknown, single	12	Moderate differentiated	Radiation therapy
(39)	2012	72	Male	Alcohol	Medial pterygoid muscle	3.5×2.2 cm, single	0	Moderately differentiated	Chemo-radiotherapy (sorafenib)
(40)	2012	65	Male	HBV	Intercostal muscle	3.5×1.8×2.5 cm, single	24	Unknown	Surgical resection
(41)	2013	61	Male	Alcohol	Iliac muscle	5×4 cm, single	0	Unknown	Chemotherapy (doxorubicin)
(42)	2013	55	Male	HBV and HCV	Left pectoralis major, deltoid, and left teres minor muscles	Left pectoralis major (3.5 cm×1.8 cm, 2.2 cm×1.9 cm) left deltoid muscle (unknown)	60	Unknown	Chemo-radiotherapy (sorafenib)
(43)	2014	47	Male	Unknown (NBNC)	Right abdominal rectus muscle	3.5 cm×4.3 cm×5.4 cm, single	144	Moderately differentiated	Surgical resection
(44)	2014	31	Male	HBV HIV	Chest wall, pectoral muscles	Unknown	0	Unknown	Chemotherapy (cisplatin and adriamycin)
(44)	2014	36	Male	Unknown (non HBV, non HIV)	Chest wall	Unknown	0	Unknown	Chemo-radiotherapy
(45)	2017	54	Male	HBV	Disseminated skeletal muscle metastasis (right psoas muscle, bilateral erector spinae, left gluteus maximus, right gluteus intermedius muscle, and anterior abdominal wall muscles)	Left hypochondrium (10×8 cm), right lower abdomen (5×5 cm), and central lower abdomen (3×4 cm)	48	Unknown	Conservative treatment
(32)	2017	55	Male	HBV	Paravertebral muscle	3.7 cm, single	6	Moderately-poorly differentiated	Chemo-radiotherapy
(46)	2019	81	Male	HCV	Biceps femoris muscle	7 cm, single	84	Unknown	Surgical resection
(47)	2019	62	Male	Unknown	Giant hematogenous left quadricep muscle	30×14 cm, single	72	Moderately differentiated	Radiation therapy
Our case	2018	78	Male	NBNC	Teres major muscle	14×13×9 cm, single	0	Moderately differentiated	Palliative therapy

period from surgery to the discovery of muscle metastases ranged from 1 year to over 10 years. When HCC and muscle metastases are detected at the same time, similar to the present case, they are generally treated with systemic chemotherapy first.

In conclusion, we herein report a case of HCC with metastasis to the teres major muscle, which is a rare metastatic site for HCC. This is the first report of metastasis of HCC to the teres major muscle. Early washout during CEUS is consistent with a pathological diagnosis of moderately or poorly differentiated HCC rather than well-differentiated HCC. In addition, CEUS of the metastatic muscular lesion

had the same pattern of enhancement as that of the primary lesion. Rare muscular metastasis should be considered if the hepatic tumor is moderately or poorly differentiated HCC.

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

The authors state that they have no Conflict of Interest (COI).

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