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CASE REPORT

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Soleus Muscle Single Metastasis from Hepatocellular Carcinoma

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ABSTRACT

Extrahepatic metastases of hepatocellular carcinoma (HCC) are associated with poor prognosis, while such lesions in skeletal muscles are extremely rare. A unique case of skeletal metastasis in the soleus muscle in a 76-year-old male patient with HCC is reported. The patient presented with a painful palpable mass in his left calf. Magnetic resonance imaging (MRI) revealed a contrast-enhancing lesion in the soleus muscle, while core needle biopsy showed metastatic lesion from the HCC. Due to the poor overall condition of the patient, no further treatment was performed, while he passed away three months later. Hepatocellular carcinoma represents an aggressive tumor, with poor prognosis, especially in cases of extra-hepatic metastases. Such lesions have a reported incidence of about 15%. Extra-hepatic metastasis to the skeletal muscles is extremely rare, with only 21 more such cases reported in the literature so far. No clear therapeutic strategies exist for such cases. Thus, it is of utmost importance to detect similar cases in early stages for a possible better prognosis and clearer understanding of the therapeutic options, including surgical and loco-regional treatments.

Keywords: skeletal muscle metastases, soft tissue tumors, soft tissue metastases, hepatocellular carcinoma metastases, muscle tumor.

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INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) has been rapidly increasing, mainly due to the prevalence of hepatitis B and C virus. It is estimated that its incidence ranges between 250,000 and 1,000,0000 new cases *per* annum worldwide (1). It represents the fourth most common cancer-related death, leading to millions of deaths *per* year. Its biological features include the manifestation of distal metastases. Despite the advance in diagnostic and treatment methods, the five-year survival of the disease remains low at approximately 16% (1, 2).

Hepatocellular carcinoma can spread *via* either lymphatic and hematogenous route or by direct invasion. Hematogenous spread to extrahepatic sites occurs in about 50% of all cases. The lungs, adrenal glands, intestine, bones, spleen, heart and kidney are the most common sites (2, 3). Extrahepatic metastases of HCC are associated with poor prognosis (1, 4).

Metastasis of HCC to the skeletal muscle tissue is extremely rare, with just a few such cases reported in the literature so far. Extrahepatic metastases in skeletal muscles, including paravertebral, glutes, biceps and psoas muscles, though rare, have been reported (5, 6).

A unique case of a single metastatic lesion in the soleus muscle in a 76-year-old male patient suffering HCC is presented. Furthermore, a thorough literature review of these cases is provided. ❑

CASE PRESENTATION

A 76-year-old male presented to the outpatient clinic due to a painful mass in the left calf. His medical history was remarkable for HCC, which was diagnosed three years ago through needle biopsies. The HCC was located in the fourth liver segment. The patient was suffering from liver cirrhosis due to chronic hepatitis B diagnosed 20 years ago. His liver function parameters were within normal limits. Up to that point, surgical intervention, following oncologic council decision, that had taken into account the patient's general condition, was rejected and radiofrequency (RF) thermo-ablation of the tumor had been performed as treatment of choice. He had not received any other specific antineoplastic treatment. The patient was followed-up during the next three years, twice *per* year, with hematological and biochemical laboratory examination as well as chest and abdominal computed tomography (CT) scans. The remaining medical history was remarkable for diabetes mellitus and smoking (80 pack-years). His last CT scan revealed that the HCC (in the fourth liver segment) was 4.7 x 3.8 cm in size.

At this point in time, three years after the initial diagnosis, he complained for pain in the left calf, while a palpable mass was found during physical examination, which was hard and painful, while no neurovascular deficit was present. Laboratory examination revealed serum glutamic-oxaloacetic transaminase (SGOT) = 94 units *per* liter (U/L), serum glutamic pyruvic transaminase (SGPT) = 104 (U/L), alkaline phosphatase (ALP) = 477 (U/L), gamma-glutamyl transferase (γ-GT) = 689 (U/L), alpha-fetoprotein (α- FP) = 232 ng/mL, Ca19-9= 524.9 U/mL. It is

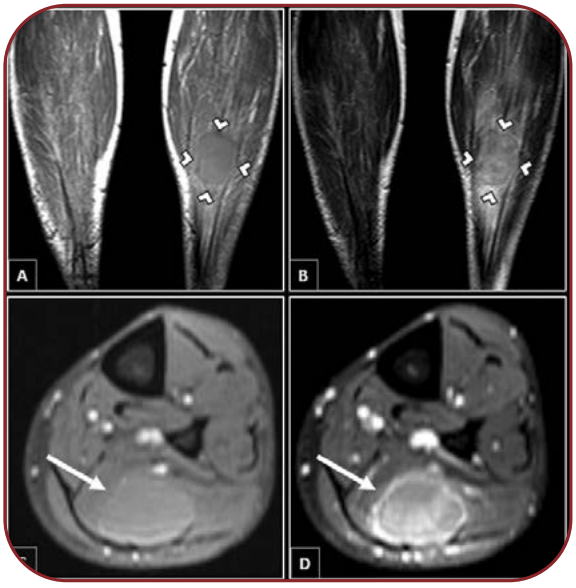

FIGURE 1. MRI examination of the lower extremities. T1-weighted non-fat suppressed coronal image (A) and T2-weighted non-fat suppressed coronal image (B) of the lower extremities demonstrate a well-demarcated intramuscular lesion located in the left soleus muscle (as indicated by the arrowheads). The lesion displays isointense signal on T1-weighted images (A) and hyperintense signal on T2-weighted images (B), when compared to the surrounding muscles. Axial fat-suppressed T1-weighted images of the left lower extremity prior to (C) and following (D) intravenous contrast (gadolinium) administration illustrate conspicuous contrast uptake of the intramuscular lesion (arrow)

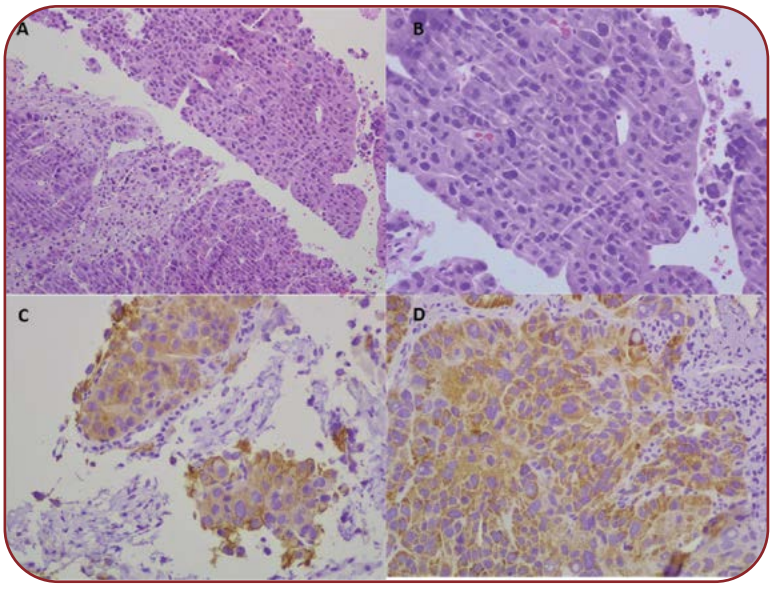

FIGURE 2. A. Carcinoma growing in a trabecular and pseudoglandular pattern (Hematoxylin-eosin stain, X100 magnification). B. Tumor cells with eosinophilic cytoplasm and large nuclei with prominent nucleoli (Hematoxylin-eosin stain, X200 magnification). C. Positive staining of tumor cells for cytokeratin 8/18 (X200 magnification). D. Positive granular cytoplasmic staining of tumor cells for HepPar1 (X200 magnification)

of note that the same laboratory examinations (five months ago) were within normal limits, hence the disease was considered to be in progression.

Magnetic resonance imaging (MRI) of the left tibia revealed a contrast-enhancing 48 x 29 mm lesion in the soleus muscle (Figure 1). Due to the non-specific imaging characteristics of the lesion, further investigation through histology was dictated. Hence, a core needle biopsy was performed to rule out sarcoma or some other neoplastic entity. Histologically, fragments of a malignant neoplasm were seen among few small fragments of fibrous tissue. The neoplastic cells formed trabeculae, large nests or pseudoglandular structures (Figure 2A). They were large, epithelioid, with abundant eosinophilic cytoplasm and large, ovoid, round or irregularly shaped nuclei and prominent nucleoli (Figure 2B). The morphology was suggestive of carcinoma. On immunohistochemistry, the tumor cells were positive for cytokeratins (CK) 8/18 (Figure 2C), confirming their epithelial nature implied by the morphology. Hepatocyte Parafin 1 (HepPar1), a sensitive and specific marker of hepatocytic origin, was also positive in a granular cytoplasmic pattern (Figure 2D). Tumor cells were negative for two other hepatocytic markers, arginase and glypicane-3, as well as for CK20 and CK19, CDX2 and TTF-1. Hence, the diagnosis of metastatic hepatocellular carcinoma was rendered.

The patient was started on palliative analgesic treatment, including epidural analgesia. Three months after the biopsy of the metastatic lesion, the patient passed away due to hepatic failure by the progression of HCC and cirrhosis, general weakness and asthenia. ❑

DISCUSSION

By 2030, mortality due to HCC is estimated to exceed one million people *per* annum worldwide. Hepatocellular carcinoma is a relatively common primary hepatic malignancy ranked sixth regarding incidence of all malignancies, while it is an aggressive tumor, ranked fourth in mortality rate (3). Survival in patients with HCC has been increased during the last decades due to advanced diagnostic techniques and treatment methods. Treatment may include either local interventions such as surgical excision, radiofrequency ablation, trans-catheter arterial chemoembolization (TACE), yttrium-90 microspheres, liver transplantation or systemic treatment with classical modalities such as chemotherapy and radiotherapy, while a number of new agents has given further promising results (1, 3).

Extra-hepatic metastatic lesions have a reported incidence of about 15%, while there are more frequently being reported due to improvement in survival (2). Extra-hepatic metastases to the skeletal muscles are extremely rare, since the lungs, lymph nodes and bones are the most common sites (4, 6). The present report describes a unique case of such an extra-hepatic metastatic lesion in the soleus muscle.

A meticulous electronic search of the PubMed, Medline and EMBASE databases revealed another 21 cases of extra-hepatic metastases in skeletal muscles, none of which included the soleus muscle (2, 4-22). Table 1 highlights the main characteristics of these cases. The patients' mean age was 58.1 [standard deviation (SD)= 14.4], while most of them were males (19; 90.5%). In 10 (47.6%) cases, other metastatic lesions co-existed, four of them were extra-hepatic lesions (40%). Multiple muscles have been reported as extra-hepatic metastatic re-

TABLE 1. Main characteristic of all cases with muscular extra-hepatic metastases from HCC reported in the literature

Author	Year	Gender/ Age	Primary tumor treatment	Skeletal muscle metastasis	Other metastases	Treatment of muscle lesion
Verhoef C *et al* (7)	2005	F/39	Excision	Chest wall	None	Excision
Wu MH *et al* (8)	2006	M/50	Excision	Psoas muscle	None	Excision
Young C *et al* (9)	2007	M/53	None	Gluteus maximus muscle	None	Excision
Masannat YA *et al* (10)	2007	M/63	Excision	Gastrocnemius muscle	None	Excision
Onen A *et al* (11)	2008	M/52	Liver transplantation	Chest wall	None	Excision
Yau T *et al* (12)	2008	M/54	Excision	Rectus femoris muscle	Lungs	Kinase inhibitor (Sorafenib)
Sirigu D *et al* (13)	2009	-/62	Transcutaneous chemoembolization, excision	Pectineal muscle	Multiple intrahepatic HCC	-
Sano T *et al* (14)	2009	M/82	Excision	Diaphragm	None	Excision
Michalaki V *et al* (15)	2011	M/70	Excision	Humorous muscle	None	Excision
Jiang H *et al* (16)	2012	M/44	Excision	Extraocular muscle	None	Radiotherapy
Yu S *et al* (17)	2012	M/72	None	Medial pterygoid muscle	Multiple intrahepatic HCC	Radiotherapy
Furumoto K *et al* (18)	2012	M/65	RF ablation, transcutaneous chemoembolization	Intercostal muscle	None	Excision
Subramaniam N *et al* (19)	2013	M/61	None	Iliac muscle	Diffuse intrahepatic HCC	Chemotherapy
Jo S *et al* (20)	2013	M/55	Excision	Pectoralis major deltoid, teres minor	Brain metastases	Radiotherapy
Traficante D *et al* (21)	2014	M/47	Excision	Rectus femoris muscle	None	Excision
Shah M *et al* (22)	2014	M/31	Chemotherapy	Chest wall, pectoral muscles	Multiple intrahepatic HCC	Chemotherapy
Shah M et al (22)	2014	M/36	Chemotherapy, radiotherapy	Chest wall	Peripancreatic region, brain, cervical lymph nodes	Chemotherapy, radiotherapy
Takahashi K *et al* (2)	2017	M/55	Excision	Paravertebral muscle	Multiple intrahepatic HCC	Radiotherapy
Orita *et al* (6)	2019	M/81	Excision, transcutaneous chemoembolization	Biceps femoris muscle	Lungs	Excision
Song Q *et al* (4)	2021	M/70	Liver transplantation	Vastus lateralis	None	Excision
Nakayama A *et al* (5)	2022	M/78	Radiotherapy	Teres major	Multiple intrahepatic HCC	Radiotherapy

gions; the most common ones seem to be the chest wall in four (19%) cases and rectus femoris muscle in two (9.5%) cases. Surgical resection of the metastatic skeletal muscle lesion was performed in the majority of cases (11 cases; 52.4%).

HCC patients with extra-hepatic metastases have poor prognosis and their survival is 4% at five years, 20% to 30% at one year and approximately 7% at three years (1, 17, 20). It is also of note that no standardized treatment exists for these patients.

Sorafenib, a kinase inhibitor, has exhibited some improvement in patients with advanced HCC (12). Nevertheless, it has been shown to offer only about three-month improvement. Furthermore, systemic cytotoxic chemotherapy agents such as adriamycin, fluorouracil and cisplatin are palliative treatment options for advanced HCC and have low response rates. Other options, including capecitabine, regorafenib, c-Met inhibitor and check point inhibitors appear to be promising, but experience with some of these agents is yet rather limited (2, 23).

Aggressive surgery for extra-hepatic metastases has been proposed as treatment option in order to reduce tumor-burden. Patients with T1 or T2 primary tumor with less than two extrahepatic lesions may be candidates for this therapeutic strategy (23, 24).

In the present patient, the overall condition was already poor and therefore, surgical resection of the muscular metastasis was not decided. He was commenced on palliative care, mainly with analgesics until his death, three months after the diagnosis of the metastatic lesion.

Bones represent a common site for HCC metastases; however, muscle metastases are rare. This may be due to a couple of factors, including that, 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, making it unsuitable for tumor cell circulation (4-6). Furthermore, lactic acid produced by skeletal muscles as well as the local pH environment suppresses tumor cell growth, while muscles also encompass proteases and other inhibitors, suppressing tumor invasion and expansion (25).

More recently, skeletal muscle metastases have been more commonly reported, probably not only as a result of the multidisciplinary approach in the treatment of these patients but also because of more sensitive imaging techniques such as positron emission tomography-computed tomography (PET-CT) that may locate such lesions in early stages (23, 25).

The most common tumors with muscle metastases originate from the thyroid, esophagus, stomach, pancreas, colon, rectum, bladder, breast, ovary and prostate, while the most common sites of muscle metastases are the erector spine, iliopsoas, and paravertebral muscles (25). Spread is considered either hematogenous or iatrogenic through biopsy of the primary lesion. In the reported patient the spread most probably was hematogenous, since no procedures had been performed in the area (25).

Multiple imaging techniques, such as plain radiographs, CT, MRI and PET-CT, have been used for diagnosis and staging of soft tissue lesions, the most well-known being radiography (X-rays), CT, ultrasound (US) and MRI (25). X-rays might be able to diagnose unanticipated skeletal abnormalities/deformities mimicking the presence of a soft-tissue mass and may also be diagnostic in specific cases (26). Computed tomography can readily detect the presence of calcifications and characterize mineralization and its specific patterns, which can be useful in cases where radiographs may prove nonspecific. Nevertheless, CT has the additional capability of multiplanar reconstructions, which can aid in the detection and characterization of possible bony cortex remodeling/invasion from the neighboring soft-tissue lesion (25, 26).

Furthermore, US has progressively gained an increased role in the initial diagnostic approach of soft-tissue masses (26). It seems to be most valuable in the assessment of superficially located small lesions and in the differentiation of cystic from solid masses; however, its role in the evaluation of deeply located lesions seems to be more limited. In addition, due to its availability and low cost, US is widely acknowledged as the principal imaging modality for guiding biopsy of soft-tissue masses (20, 26).

Magnetic resonance imaging is still considered the modality of choice for diagnostic and local staging purposes of musculoskeletal soft-tissue masses. Musculoskeletal soft-tissue lesions can be sufficiently assessed with T1-weighted sequences and fluid-sensitive images with fat suppression. Proton-density–weighted fast spin echo (FSE) images with fat suppression may have an increased signal-to-noise ratio compared to T2-weighted (FSE) images with fat suppression (26). Alternatively, gradient-echo (GRE) sequences are less sensitive to fluid in comparison to the aforementioned techniques but are more capable of detecting previous intralesional hemorrhages due to their superior susceptibility to hemosiderin and artifacts. On the other hand, STIR (short TI inversion-recovery) sequences are more prone to motion artifacts but augment lesion detection and may also be valuable in areas displaying inhomogeneous fat suppression (26).

However, tissue sampling is of utmost importance for definite diagnosis. Differential diagnosis of skeletal muscle metastases mainly refers to soft-tissue sarcomas (2, 6, 25).

Skeletal muscle metastases from carcinomas frequently present as painful palpable masses with or without swelling and are commonly found before diagnosis of the primary carcinoma (11, 17).

Therapeutic management is mainly based on the treatment of the primary tumor, while local

interventions,such as radiotherapy or surgery are performed in cases of symptomatic lesions that fail to respond to basic primary tumor treatment (1, 25). ❑

CONCLUSIONS

A unique case of metastatic lesion in the soleus muscle from HCC has been reported. Muscle metastases from HCC are extremely rare, and thus, treatment is still obscure. More data and research are necessary to conclude upon the optimal treatment, including surgical options and loco-regional therapies. Furthermore, such cases should be taken into account, in order to be detected in early stages through a high suspicion index and proper imaging modalities, which could lead to better prognosis. ❑

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