Left gluteal metastasis from a hepatocellular carcinoma – an unusual finding

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Abstract
Hepatocellular carcinoma (HCC) is the primary malignant tumor of the liver that is directly derived from parenchymal cells. It is usually encountered in patients already suffering from a long-established liver disease that has evolved past the stage of liver cirrhosis. It is usually associated with viral liver infections, alcohol consumption or other dietary habits that lead to liver damage. Metastases are not rare and are usually found incidentally after a period of monitoring the main liver disease. We present here a rare case of HCC metastasis found in the right gluteal region, in a hepatitis C virus-infected patient also displaying lung tumor lesions. Diagnosis of both the metastasis and of the primary tumor were found during the same hospital visit, employing contrast-enhanced computed tomography, magnetic resonance imaging and ultrasound (US), with positive biopsy of the metastatic lesion, performed under US guidance. The patient received oncological treatment, with good prognosis and stable evolution during the next eight months since diagnosis.

Keywords: hepatocellular carcinoma, gluteal metastasis, lung metastasis, immunohistochemistry, differential diagnosis.

Introduction
Hepatocellular carcinoma (HCC) is a malignant epithelial tumor with origins in the hepatic cells. It is the most frequent type of primary hepatic malignancy, occurring mostly in patients who suffer from hepatitis C virus [1, 2]. It is also one of the major causes of death among these patients. It is the sixth most frequent type of cancer worldwide (749 000 new cases/year) and the third cause of death by cancer (692 000 cases/year) [1–3].

The incidence varies from 3/100 000 in Western countries to more than 15/100 000 in certain endemic regions and it is directly correlated with the geographical distribution of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, recognized as the most important causes of chronic liver disease and consequently HCC [2–4].

The occurrence of the hepatocellular carcinoma is associated with a series of predisposing factors. HCC is more frequent among males, old age also being associated with an increase predisposition. Viral liver disease, exposure to exogenous toxins (aflatoxins or alcohol abuse), metabolic factors (obesity, hepatic steatosis, hemochromatosis, type 2 diabetes mellitus) or congenital disorders (either alpha-1 antitrypsin deficiency, Wilson’s disease or hemophilia) are also strongly associated with HCC development [5–8].

The frequency of HCC among the patients who suffer from hepatic cirrhosis is reported to range between 1% and 7% [1–4, 9]. Hepatitis C chronic infections that are left untreated lead to hepatic cirrhosis in the majority of cases, and the risk of HCC is of 14.4%. Literature cites HCC development in approximately 20% of the patients diagnosed with liver cirrhosis, at an average time interval of 30 years and in 1–5% of the patients infected with the hepatitis C virus [9, 10].

A growing body of evidence directly correlates the “metabolic epidemic”, an emerging threat especially in the Western countries due to unhealthy dietary habits, and liver disease. An interesting correlation was established between non-alcoholic liver disease leading to cirrhosis, diabetes and the early development of HCC [11, 12]. Mechanisms related to fibrosis, especially involving liver stellate cells and the altered environment created by pro-fibrotic conditions also seems to favor tumor development in the affected liver [13, 14].

The difficult differential diagnosis of the premalignant dysplastic lesions is usually aided by pathology. The invasion of the stromal cells or the invasion of the cancer cells inside the portal triads or inside the fibrous septa define HCC and are not found in the dysplastic lesions [15]. Nevertheless, other histological features can also be observed in dysplastic lesions [16]. Multiple immunohistochemical (IHC) stainings are available and even computer-aided techniques have shown promising results.
in diagnosing and establishing prognosis in HCC patients, especially when correlated with clinical and laboratory findings [17]. However, the latest protocols used for diagnosis and staging employ contrast-enhanced imaging methods, as obtaining positive biopsy from the liver may pose the risk of dissemination by needle or possible false-negative reports. Interpreting contrast uptake during the main physiological phases, either performed by the operator or aided by computerized semi-automatic techniques, can greatly enhance diagnostic accuracy, especially in centers that experience lower incidence of the disease [18, 19].

As modern diagnostic techniques and treatment options become increasingly available, the survival rate of HCC patients increases. Thus, a larger number of metastases are found, hence the possibility to encounter more unusual sites of extrahepatic dissemination [20]. Even in this context, muscle metastases remain rare, with only a few cases not related to needle dissemination being reported in cohort studies [21].

**Aim**

We present the rare case of a male patient diagnosed with a rare form of metastasis from HCC, highlighting the diagnostic procedures and the importance of immuno-histochemistry in establishing the origin of the secondary tumor.

**Case presentation**

We present the case of a non-smoking 69-year-old patient with rural residence. He provided informed consent in writing upon admission as part of the standard procedure, following the recommendations of the Ethical Boards of both the University of Medicine and Pharmacy of Craiova, and the Emergency County Hospital of Craiova, Romania. All relevant medical data, exclusive of any personal identifying information, were collected in accordance with national and international legislation and guidelines.

He was a former farmer, known with hepatitis C viral infection for 10 years and who underwent hepatoprotective treatment, with no other significant morbidity. He was referred to the Clinic of Gastroenterology accusing pain in the right hypochondriac region, tegumentary pruritus and asthenia.

The patient also described a self-perceived subcutaneous tumor mass in the left gluteal region, measuring approximately 8/11/13 cm, solid upon local examination, painless on palpation, with irregular margins, adherent to subjacent tissues and having normal covering tegument. Affirmatively, the tumoral development appeared after intense physical effort that the patient had performed eight months before and showed some improvement after self-administered anti-inflammatory therapy. The patient noticed not only the decrease in the painful lumbar symptomatology, but also a decrease in the dimensions of the tumor and in the local inflammatory phenomena.

Clinical examination showed normally hydrated, slightly palid teguments, with skin lesions located on the front and back of the chest, on the abdomen and inferior limbs, the left gluteal tumor previously described, balanced cardiorespiratory system, liver with the inferior margin at 3 cm under the costal margin, of slightly increased consistency, sensitive on palpation, impalpable spleen and reported polakiuria.

The biological examination revealed increased values for aspartate transaminase (AST) 133.9 U/L, alanine aminotransferase (ALT) 127.5 U/L, gamma-glutamyltransferase (GGT) 148 U/L, alkaline phosphatase 111 U/L, an inflammatory syndrome – erythrocyte sedimentation rate (ESR) at one hour 50 mm/h, with no anemic syndrome – hemoglobin (Hb) 13.6 g/dL, and with thrombocytopenia – 86 000/μL. The anti-HCV antibodies had a titer of 26.38 cutoff index (COI), and from the tumor markers we retain the alpha-fetoprotein (AFP) of 3577 ng/mL, neuron-specific enolase (NSE) 15.34 ng/dL and CYFRA 21-1 (cytokeratin 19 fragments) 2.96 ng/mL.

Abdominal ultrasound highlighted within the liver segments VII/VIII, near the inferior vena cava, an oval area with a hyperechoic, inhomogeneous structure, with peripheral halo of 3/2.4 cm that seemed to invade the right hepatic vein. The left liver lobe was 10 cm, right lobe 16 cm, irregular margins, with intensely diffuse inhomogeneous structure, aspect specific of cirrhosis. We decided to follow with abdominal contrast-enhanced ultrasound (CEUS); after the administration of 2.4 mL contrasting agent (SonoVue, Bracco Imaging, Switzerland), the hepatic tumor showed inhomogeneous and complete early arterial contrast uptake, more intense and precocial than the hepatic parenchyma. In the portal phase, the tumor was isocapant, and in the tardive phase, it presented incomplete tardive “wash-out”, suggestive aspect for HCC.

We performed a magnetic resonance imaging (MRI) of the abdomen and pelvis to evaluate the gluteal tumoral formation. After injecting the contrast agent, we found an inhomogeneous, gadophil tissue mass in the left gluteal region measuring 8.8/11.3/13.2 cm, with edema and osteolysis in the sacrum and on the same side of the wing of ilium. It also showed infiltration of the adjacent soft parts, prevertebral muscles and gluteal muscles (Figure 1, A and B). The liver had an irregular form, and showed two rounded focal tumors measuring 5.76 cm and 2.93 cm. We found normal signal and heterogeneous signal after the injection of the contrast agent, with hemorrhagic areas inside the larger lesion, with an intense collection in the arterial phase and washout in the tardive phase, with aspect of a possible HCC (Figure 2). We could not exclude the secondary hepatic determinations and the presence of adenopathy in the hepatic hilum with a maximum dimension of 1.69/0.7 cm.

Consequently, this was a diagnostic challenge as the differential diagnosis between a HCC with secondary hepatic determinations or a gluteal sarcoma had to be established.

In the aid of giving the diagnosis, we performed musculoskeletal echography that highlighted in grayscale a hypoechoic, multitubated image, well delimited, with sharp edges inside the gluteus maximus muscle, close to the iliac crest, which was deforming the superficial soft tissues (Figure 3A). Power Doppler examination revealed intense, diffuse, anarchic signal inside the lesion (Figure 3B). Puncture–aspiration–injection followed by reaspiration revealed no significant information, thus automatic core needle biopsy using a Bard® Magnum® gun (Bard, Arizona, USA) was performed, obtaining four samples from the gluteal lesion for histopathological (HP) and IHC examination. The biopsy was performed with local anesthesia, both at the skin entry and near lesion, with a 14G needle, after preliminary scanning the area of
entrance to identify the appropriate approach. The skin was cleared using specific asepsis protocol and then was cut using a disposable surgical blade No. 24, to introduce the needle tip, which was advanced into the lesion under US guidance. The position of the needle tip was confirmed at the level of the lesion by US examination in two planes and the cutter was then deployed. We harvested four tissue fragments and placed them in a formalin container for the HP and the IHC stainings. We fixated the biotic material with 10% formalin and included in paraffin.

The HP evaluation highlighted tissue fragments of variable dimensions (from 1 to 6 mm) with a microscopic structure of hepatic parenchyma. Enlarged epithelial cells displayed slightly rounded or polygonal shapes, with eosinophilic cytoplasm, rounded nucleuses and dispersed chromatin. We observed tumoral cells laid in trabeculae or islands, separated by a conjunctival richly vascularized capillary stroma. Further examination revealed relatively rare mitoses and fibrosis that shaped a nodular structure with reduced focal chronic infiltrate (Figure 4, A–D).

Figure 1 – MRI of the left gluteal mass, showing an inhomogeneous, intensely gadophil mass, displaying edema and osteolysis of the sacrum and iliac crest, with invasion of soft parts and paravertebral and gluteal muscles: (A) Cross-sectional image; (B) Sagittal view.

Figure 2 – MRI of the liver, showing the primary heterogeneous HCC lesions, arterial contrast uptake and late washout, characteristic of primary liver tumors derived from hepatocytes.

Figure 3 – Grayscale (A) and Doppler (B) ultrasound examination of the left gluteal mass.

Figure 4 – We could observe the trabecular placement of tumoral cells (A) and islands (B), separated by a conjunctival richly vascularized capillary stroma (A). Hematoxylin–Eosin (HE) staining, ×100.
We further performed IHC stainings, employing the Avidin–Biotin complex (ABC) method. We used the following antibodies: AFP, vimentin, carcinoembryonic antigen (CEA), Ki67, cytokeratin (CK) 8/18, CK7 and OCH1E5 (mouse monoclonal hepatocyte-specific antigen).

The IHC analysis showed negative AFP in the tumoral cells and positive vimentin in vessels. We found negative vimentin and CEA in the tumoral cells. However, we identified positive Ki67 signal in approximately 15% of the tumoral cells (Figure 5), diffuse positive OCH1E5 in the tumor cells (Figure 6, A and B), also diffuse positive CK8/18 within the tumor (Figure 7, A and B) and negative CK7 (Figure 8).

After microscopy examination, the diagnosis was of metastatic trabecular hepatocellular carcinoma.

A chest computed tomography (CT) scan was considered convenient for the evaluation of the neoplastic extension; this emphasized the multiple pulmonary bilateral nodules (Figure 9, A and B) with a maximum dimension of 1.12 cm, acknowledged as secondary pulmonary determinations, as well as an adenopathy of up to 12 mm (right paratracheal lymph nodes, the Barety segment, supracranial and infracranial).

Hence, taking into consideration the suggestive aspect of the multifocal HCC, emphasized by the MRI and by CEUS, AFP of 3577 ng/mL, and the pathology exam of the tumoral gluteal formation, we established a diagnosis of HCC with muscular and pulmonary determinations.

Figure 4 (continued) – We could observe the trabecular placement of islands (C and D), separated by a conjunctival richly vascularised capillary stroma (C). HE staining, ×200.

Figure 5 – We observed positive nuclear Ki67 signal in some of the tumor cells. Anti-Ki67 antibody immunostaining, ×100.

Figure 6 – (A and B) Immunostaining with OCH1E5 marker showing diffuse signal. Anti-OCH1E5 antibody immunostaining, ×100.
The patient was initiated in September 2017, with Sorafenib 200 mg film-coated tablets given at 800 mg/day – two capsules in the morning / two in the evening. Until now, the patient continues with Sorafenib without significant adverse events.

AFP levels progressively decreased over the course of nine months, down to a value of 130.3 ng/mL in June 2018. Regarding the biological condition, the latest results of the analysis performed on in June 2018 revealed ALT 131.01 U/L, AST 125.79 U/L, GGT 143.26 U/L and normal blood counts.

The patient so far tolerated the treatment well, without changing the general state. The last imagistic investigations carried out on March 2018 revealed the presence of...
metastasis of the psoas muscle [24] and there is a report et al. [11] that were diagnosed as extrahepatic disseminations from HCCs. One such case was presented by Gilsanz Fernández and consecutive immunohistochemistry playing a key role. sarcoma or hepatocellular carcinoma with muscular dissemination may pose a challenge, as it is an unusual occurrence. The sarcomatous aspect of the left gluteal formation presents a challenge; however, the biological status of the patient and the history of the chronic hepatitis C point to a different diagnosis. In such cases, both the HP and the IHC analysis are the ones to establish the diagnosis.

We used cross-sectional contrast-enhanced imaging to diagnose the primary liver tumor; as CEUS is available in our Center and no major side effects or contraindications exist for the contrasting agent, we decided to perform this investigation as well in order to confirm the diagnosis. The CT further aided in staging as it highlighted the secondary lung tumors.

However, we diagnosed the left gluteal formation after we performed the pathology analysis on the biopsy specimens obtained under ultrasound guidance from the left gluteal formation of the patient, even though identified by imaging. This posed an important diagnostic challenge, as muscle HCC metastases are rare [22].

There are few reports in the literature of gluteal masses that were diagnosed as extrahepatic disseminations from HCCs. One such case was presented by Gilsanz Fernández et al., in 1989 [23], and remains one of the few cases found in literature. Another case describes an unusual metastasis of the psoas muscle [24] and there is a report from Yau et al., citing a late development of an intramuscular metastasis in the left thigh [25], in a patient that progressed slowly and benefited from surgical treatment of the primary liver tumor. Recently, a group of authors report two musculoskeletal metastases of HCC, one of them at the gluteus maximus level [26]. Ours is, to our knowledge, one of the first reports that also shows data after initial treatment with Sorafenib for the primary lesion, initiated after the incidental discovery of the metastasis.

Some cohorts cite a very low incidence for muscle HCC metastases; for instance, one recent study on 995 consecutive cases diagnosed with HCC and followed at regular intervals only revealed one muscle metastasis from 151 patients that presented metastases (0.7% incidence) [27]. Another retrospective cohort that followed 482 HCC cases over a period of six years only identified one muscle metastasis [28]. Most of these studies link the increased number of metastases to increased survival due to modern treatment options and the refinement of protocols based on imaging; however, our case did not benefit from HCC or antiviral treatment. The gluteal self-perceived mass was one of the presenting symptoms, thus adding to the rarity of the finding and the need for thorough pathology investigation.

Discussions
A clear differential diagnosis between left gluteal sarcoma or hepatocellular carcinoma with muscular metastasis may pose a challenge, as it is an unusual occurrence. The sarcomatous aspect of the left gluteal formation presents a challenge; however, the biological status of the patient and the history of the chronic hepatitis C point to a different diagnosis. In such cases, both the HP and the IHC analysis are the ones to establish the diagnosis.

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Conclusions
To sum up, the certain diagnosis of this patient was not possible without the myriad of clinical investigations, due to the fact that the main sign of HCC, in this case is represented by a tumoral gluteal formation. The patient considered it a result of physical effort, lacking any other significant symptoms. The difficulty in stating the diagnosis consists of the aspect of the MRI that initially states the sarcomatous aspect of this gluteal formation and the history of the patient that suffers from hepatitis C virus in association with the hepatocytolysis syndrome and the increased titer of the alpha-fetoprotein. The differential diagnosis was decided between left gluteal sarcoma and metastatic hepatocellular carcinoma, pathology and consecutive immunohistochemistry playing a key role.

Conflict of interests
The authors declare that they have no conflict of interests.

Author contribution
Alina-Maria Balea and Ananu Florentin Vreju had an equal contribution in preparing the manuscript and share first authorship.

References


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