

## CUTANEUS AND SUBCUTANEUS METASTASIS FROM HEPATOCELLULAR CARCINOMA - REPORT OF THREE CASES

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Hepatocellular carcinoma (HCC) is the third most common cause of death from all cancers. Metastases of HCC in the skin are very rare and account for only 0.8% of all known cutaneous metastases.

We here present three cases of HCC with metastases in the skin and subcutaneous tissue, which was the first manifestation of the tumor. The diagnosis was based on the characteristics of histomorphological appearance and testing of the immuno-phenotype of tumor cells. In all three cases, within the metastatic tumors, a strong immunohistochemical expression of AE1/AE3, EMA and HepPar1 was confirmed. In two cases, elevated serum levels of AFP were found.

In any diagnosis of cutaneous malignant tumor it is, first of all, important to distinguish any secondary deposits in the skin from the usual skin neo-proliferations. HepPar1 is an excellent marker of hepatocellular differentiation which significantly facilitates the diagnosis of metastatic hepatocellular carcinoma.

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**Key words:** Hepatocellular carcinoma, skin metastasis, initial presentation

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### Introduction

Hepatocellular carcinoma is the most common primary malignant tumor of the liver and makes up 7% of all malignant tumors in humans. It is the sixth most common malignant tumor, with the highest incidence in East Asia (China, Korea, Taiwan and Japan) and Western and Central Africa. During 2012, 782,500 new cases of liver cancers were reported worldwide (1, 2) The incidence rate in the USA is growing progressively and in the period between 1975 and 2011, a growth from 2.6 per 100,000 to 8.6 per 100,000 was observed (3).

The increasing incidence of HCC is directly correlated with an increased frequency of hepatitis B (HBV) and hepatitis C virus (HCV) infection (4, 5). It has been also estimated that there is an association of HCC with exposure to aflatoxin, autoimmune hepatitis, steatohepatitis and primary biliary cirrhosis and sclerosing cholangitis (6-8). Some two decades ago it was observed that liver cirrhosis was present in approximately 80-90% of diagnosed patients and it presented the most important risk factor for the occurrence of HCC (9). Other risk factors include chronic alcoholism, cigarette smoking, hemochromatosis and much rarer tyrosinemia (4-6).

Hepatocellular carcinoma often invades blood vessels which can lead to extensive intra - and extra-hepatic metastases, usually to the lungs, lymph nodes, bones, kidneys and adrenal glands (10). In this report we examined a case of HCC with cutaneous metastases and two cases of HCC manifested by multiple tumor formations in the subcutaneous tissue. In all three cases, the initial clinical presentation of HCC was the skin and/or subcutaneous tissue involvement.

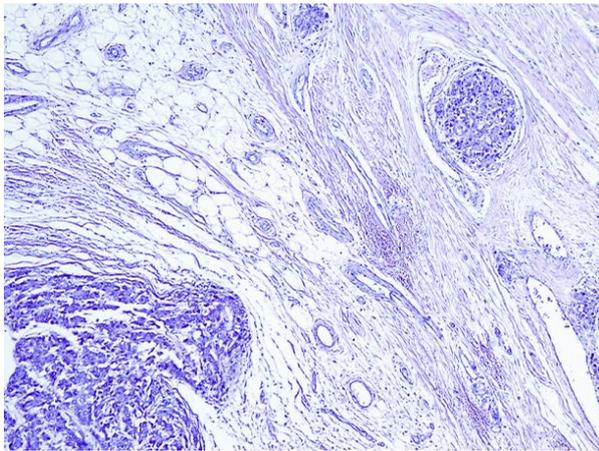
### Case reports

#### Case No 1

A male patient, aged 63, was referred to a surgeon due to an ulcerative skin tumor on the parietal region of the scalp. The change had been noticed 3

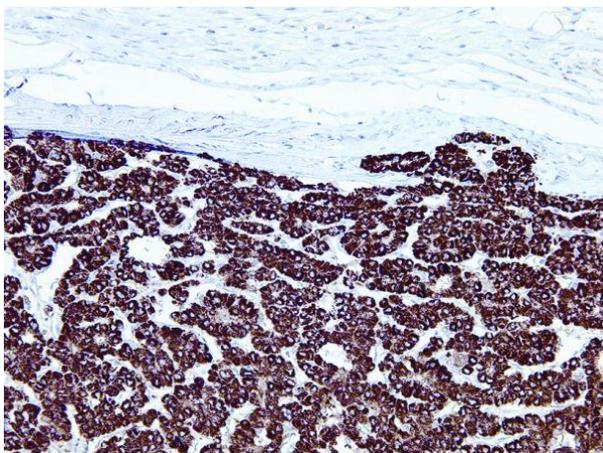
months before he came to the doctor. He described a rapid and constant growth of the tumor.

The resected material was a fragment of skin and subcutaneous tissue, 40 x 27 x 15mm in size, on the surface of which there was an ulceration. The bottom of the ulceration consisted of whitish homogeneous, solid tumor tissue, 25 x 15 x 12mm in size. It was established by histopathological examination that the resected skin and subcutaneous tissue was infiltrated with tumor cells organized in solid clusters and rare adenoid formations. The tumor cells were medium large, atypical, round and polygonal, with abundant, bright, eosinophilic cytoplasm and irregular, hyperchromatic and large nuclei with prominent nucleoli. The stroma of the tumor was scanty. Mitosis were numerous. Tumor growth was infiltrative. Necrosis was present in the tumor tissue (Figure 1).



**Figure 1.** HCC metastases in the skin (HE, 100x)

The tumor cells had the following immunohistochemical profile: EMA (Figure 2), AE1/AE3, CK7 and HepPar1 – positive.



**Figure 2.** Moderate to strong expression of EMA in the cells of metastatic HCC in the skin (IHC, 40x)

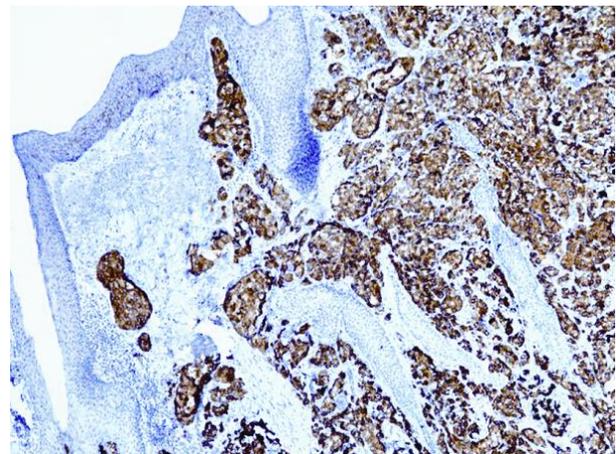
After the performed analysis, a metastasis of hepatocellular carcinoma in the skin was suspected.

As part of the examination, magnetic resonance imaging of the abdomen, bone scintigraphy and chest CT were carried out. After the radiological examinations, a solitary liver tumor, 6cm in diameter, was observed, as well as the changes in the ninth and tenth thoracic and second lumbar vertebra, that corresponded to secondary deposits. Blood analysis and biochemical tests were within normal values. AFP level was higher than normal. The patient underwent oncological treatment; the death occurred 8 months after the hepatocellular carcinoma was first diagnosed.

#### Case No 2

A male patient, aged 61, was referred to a surgeon due to a subcutaneous tumor on the back, which he had noticed two months earlier, explaining its growth as being progressive.

The patient was treated for tuberculous spondylitis 15 years ago. During the surgical intervention, an unresectable tumor was noticed, and after the biopsy, the material was sent for histopathologic analysis. The obtained sample contained tumor tissue that contained adenoid, trabecular and solid arrangements of large, atypical, cubical and round cells with abundant, bright cytoplasm (eosinophilic or "empty") and irregular, moderately pleomorphic nuclei with prominent nucleoli. The stroma of the tumor was scanty. As it was a case of tumor tissue with malignant morphological characteristics, suspected as being a metastatic deposit, an immunohistochemical analysis of the tumor tissue was performed. The immunohistochemical profile of the tumor tissue was: EMA, AE1/AE3, HepPar1 (Figure 3) - positive.



**Figure 3.** High expression of HepPar1 in the cells of metastatic HCC in the subcutaneous tissue (IHC, 100x)

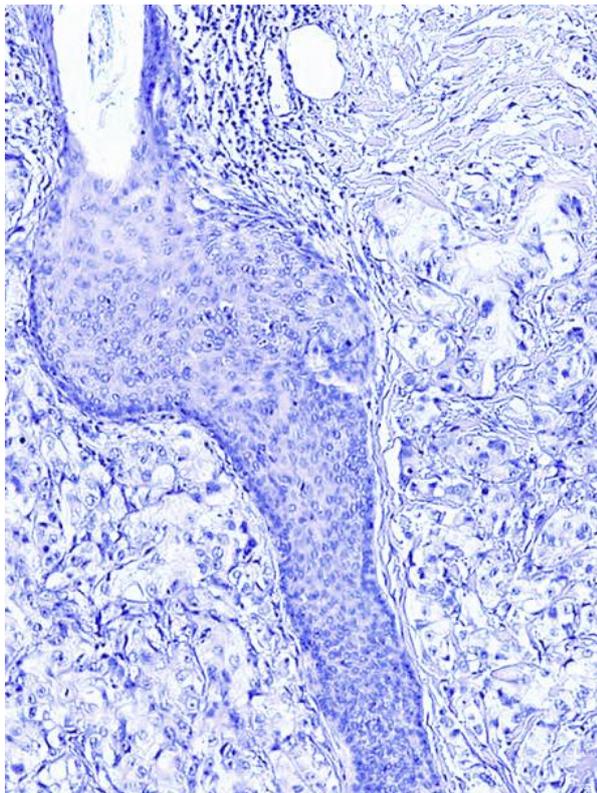
After the histopathological analysis a subcutaneous metastasis of hepatocellular carcinoma was

suspected. After the histopathological analysis, CT imaging of the chest and abdomen was conducted. The CT scan of the chest revealed a tumor mass that infiltrated the subcutaneous tissue of the back and the sixth, seventh and eighth ribs of the chest wall, with the total size of 6cm. CT scanning of the abdomen revealed a tumor in the liver of 8cm in size. The AFP level was higher than normal. The patient was referred for oncological treatment. Survival period from the time of diagnosis was 19 months.

#### Case No 3

A patient, 62 years old, was referred to a surgeon due to rapidly growing subcutaneous tumors on the scalp, parotid region of the neck and pectoral region. Due to the clinical suspicion that these may be malignant metastatic deposits in the subcutaneous tissue, a resection of the subcutaneous tumor in the pectoral region was performed. The material obtained was a whitish, firm, nodular tumor of 1.8cm in diameter.

Histopathological analysis revealed tumor tissue composed of scanty stroma and parenchyma, made up of trabecular and solidly arranged large, cuboidal, atypical cells with abundant, eosinophilic cytoplasm and large, irregular, vesicular nuclei with prominent nucleoli and numerous pathological mitoses (Figure 4). The results of an immunohistochemical analysis of the tumor tissue were: HepPar1, AE1/AE3, EMA, Vimentin - positive.



**Figure 4.** Infiltration of subcutaneous adipose tissue with metastatic HCC (HE, 40x)

After histopathological and immunohistochemical analyses, a metastasis of hepatocellular carcinoma was suspected, and it was later confirmed by radiological and biochemical examinations. The AFP value was within normal range. After the diagnosis, the patient lived for 6 months without any oncological therapy.

#### Histopathological examination

In all three cases, the samples of tumor tissue were fixed in 10% neutral buffered formaldehyde, routinely processed and embedded in paraffin. From the paraffin blocks, sections of 3-4µm in thickness were made, on which a routine Haematoxylin-Eosin method for histopathological analysis of lesions was applied, as well as immunohistochemical analysis.

The resected tissue samples which were used for immunohistochemical analysis were mounted on highly adherent slides (SuperFrost) and then dried at 60 °C in a thermostat for up to 24 hours. After the preparation of the sections in the PT link (Dako, Glostrup, Denmark) (reagent: EnVision Flex Target retrieval solution high pH), the further immunohistochemical staining procedure was automated. AUTO-IMUNOSTAINER LINK 48 (Dako, Glostrup, Denmark) was used. The Dako EnVision Flex System for visualization was used. Primary Dako antibodies, Flex Ready to use were applied and as a chromogen DAB (Diaminobenzidine) was used. Contrasting in haematoxylin was done manually (for 3 to 5 minutes).

#### Discussion

Hepatocellular carcinoma is the third most common cause of death from all cancers and the leading cause of death in patients with liver cirrhosis (11, 12, 13). It has an aggressive clinical course and it usually spreads by direct extension into the lumen of the portal vein branches and/or the lumen of hepatic veins. About 30% to 50% of hepatocellular carcinomas develop extrahepatic metastasis (14), most frequently to the lungs, lymph nodes, bones and the adrenal glands (10, 11). In recent years numerous reports have indicated an unusual behaviour of metastatic hepatocellular carcinoma (15-17). This is primarily related to the localization of extrahepatic metastasis, and various authors have described the presence of metastases in the maxillary sinus (15), orbit (16), zygomatic bone (18), mandible (19), parotid gland (20), larynx (21), subcutaneous tissue and skin (22, 23). Subsequently, extrahepatic metastases are often the initial manifestation of hepatocellular carcinoma (18, 19, 21) as was the case with all our three patients, whose first symptoms of hepatocellular carcinoma were related to the presence of metastases in the skin and subcutaneous tissue. The skin is a relatively unusual metastatic site; it is believed that less than 10% of all malignant tumors of the internal organs metastasize to the skin (1, 24) Cutaneous metastases most often originate from cancers affecting the breast and lungs, as well as from melanoma (25). Metastasis of hepatocellular carcinoma in the skin are very rare and are estimated to account for only 0.8% of

all known cutaneous metastases (26), but one should bear in mind that most evaluations are based on autopsy findings or on sporadic case reports.

Cutaneous metastases of hepatocellular carcinoma are usually localized in the head and neck region, and rarely on the shoulders and on the trunk (27, 28). Macroscopically, these present as nodules with or without ulcerations (solitary or multiple), as well as a diffuse infiltration (plaque) or as a papule accompanied by hyperpigmentation (29). In the first case, the metastatic tumor was a nodule localized in the parietal part of the scalp and there was an ulceration on the surface of the skin. In the second case, the metastatic tumor presented as a diffuse infiltration. In our third patient, the metastases presented as multiple nodules localized subcutaneously in the areas of the scalp, parotid region and pectoral region.

The mechanism of metastasizing of hepatocellular carcinoma in the skin and soft tissues has not yet been fully clarified. It is believed that cutaneous metastases occur when the tumors spread by a haematogenous route or via implantation during surgical procedures (22), while the possibility of tumor cell seeding after percutaneous needle aspiration is highlighted (23, 30). The appearance of cutaneous metastases suggests that the metastatic disease has become generalized, indicating a poor prognosis (31). Our first patient died 8 months after he had been diagnosed. The survival time for the second patient was 19 months and the third patient died 6 months after his diagnosis.

Hepatocellular carcinoma is almost three times more common in males than females (M:F = 2.7:1). It is the second leading cause of death among men, while the average age at the time of diagnosis is 65. It has been noted that in the countries with a high risk of developing HCC, this tumor may occur even before the age of 20, while in the countries with a low risk, it occurs in the population above the age of 50 (32, 33). All three patients presented in this report were males with an average age of 62 when diagnosed. The differences in the incidence of hepa-

tocellular carcinoma in relation to sex could be the result of the prevalence of alcoholism and chronic diseases in men, but this difference is also associated with increased secretion of the cytokine interleukin-6 (IL-6) in men, which plays a major role in the inflammatory response and exerts pro-proliferative and anti-apoptotic effects (34, 35). In experiments on mice, it has been shown that estrogen inhibits the secretion of IL-6, and suggests that the "estrogen-mediated inhibition" of IL-6 reduces the risk of the development of HCC in women (36).

For a correct diagnosis of cutaneous malignant tumors, it is important to distinguish any secondary deposits in the skin from typical skin tumors. In order to confirm the diagnosis of cutaneous metastasis, a biopsy is necessary. Histopathological diagnosis of metastatic hepatocellular carcinoma can sometimes be relatively simple, with the histological appearance of bright, eosinophilic cells, forming trabecular, pseudoglandular or solid arrangements, while the presence of bile and Mallory's bodies indicates hepatocellular carcinoma (11). In most cases, histopathological diagnosis can be difficult especially as the metastatic cells are often less differentiated than those in the primary tumor. In such cases, immunohistochemical diagnosis is of great importance. HepPar1 is a relatively specific marker for hepatocytes and hepatocellular carcinoma cells. It is the G1K monoclonal antibody which recognizes a mitochondrial antigen present in normal and neoplastic hepatocytes. This marker is very helpful for the diagnosis of occult hepatocellular carcinoma with distant metastases (26).

Our three cases of hepatocellular carcinoma with metastases in the skin and subcutaneous tissue indicate the unpredictable phenotypic characteristics of the tumor, suggesting that every skin lesion should be carefully observed, whereby it is very important that the pathologist identifies a secondary deposit. HepPar1 is a marker of hepatocellular differentiation which greatly facilitates the diagnosis of metastatic hepatocellular carcinoma.

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## Prikaz bolesnika

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# KOŽNE I POTKOŽNE METASTAZE HEPATOCELULARNOG KARCINOMA - PRIKAZ TRI SLUČAJA

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Hepatocelularni karcinom (HCC) je treći najčešći uzrok smrti, imajući u vidu sve maligne tumore. Metastaze HCC u koži veoma su retke i čine svega 0,8% svih poznatih kutanih metastaza.

Mi prikazujemo tri slučaja HCC sa metastazama u koži i u potkožnom tkivu, koje su bile prva manifestacija tumora. Dijagnoza je postavljena na osnovu karakterističnog histomorfološkog izgleda i ispitivanjem imunog fenotipa metastatskih lezija. U sva tri slučaja je, u metastatskom čvoru, a kasnije i u intraoperativnoj biopsiji, verifikovana jaka imunohistohemijska ekspresija AE1/AE3, EMA i HepPar1. U dva slučaja zabeleženi su i povišeni serumski nivoi AFP.

Za dijagnozu ekstrahepatičnih metastaza važno je, pre svega, razlikovati sekundarne depozite u koži od uobičajenih kožnih neoproliferacija. HepPar1 je odličan marker hepatocelularne diferencijacije, koji znatno olakšava dijagnozu metastaza hepatocelularnog karcinoma.

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**Ključne reči:** hepatocelularni karcinom, metastaze u koži, inicijalna manifestacija