

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

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Introduction: 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.

Case reports: We present here three cases of HCC with metastases in the skin and subcutaneous tissue, which was the first manifestation of a tumour. The diagnosis was based on the characteristics of the histomorphological appearance and testing of the immunophenotype of the tumour cells. In all three cases, within the metastatic tumours, a strong immunohistochemical expression of AE1/AE3, EMA and HepPar1 were verified. In two cases, elevated serum levels of AFP were recorded.

Conclusion: In any diagnosis of cutaneous malignant tumour 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 tumour of the liver and makes 7% of all malignant tumours in humans. When it comes to frequency, it is the sixth most common malignant tumour 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 recorded.³

The increasing incidence of HCC is directly correlated with an increased frequency of hepatitis B virus infection (HBV) and hepatitis C (HCV) (4, 5). It was also estimated that there is a correlation of HCC with exposure to a fla toxin, autoimmune hepatitis, steatohepatitis and primary biliary cirrhosis and sclerosing cholangitis (6-8). Some two decades ago it was observed that liver cirrhosis is present in approximately 80-90% of diagnosed patients and it presents 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 extrahepatic metastases, usually in the lungs, lymph nodes, bones, kidneys and adrenal glands (10). In this report we examine case of HCC with cutaneous metastases and two cases of HCC manifested by multiple tumour formations in the subcutaneous tissue. In all three cases, the initial clinical presentation of HCC occurred in the skin and /or subcutaneous tissue.

Case reports

Case No 1

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

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

The resected material was a fragment of skin and subcutaneous tissue, 40x27x15mm in size, on which surface there was ulceration. The bottom of the ulceration consisted of whitish homogeneous, solid tumour tissue, 25x15x12mm in size. Histopathological examination determined that the resected skin and subcutaneous tissue was infiltrated with tumour cells organized in solid arrangements and rare adenoid formations. The tumour cells were medium large, atypical, round and polygonal, with abundant, bright, eosinophilic cytoplasm and irregular, hyperchromatic and large nuclei with prominent nucleoli. A stroma of the tumour was scanty. Mitosis were numerous. Tumour growth was infiltrative. Necrosis was present in the tumour tissue (Figure 1).

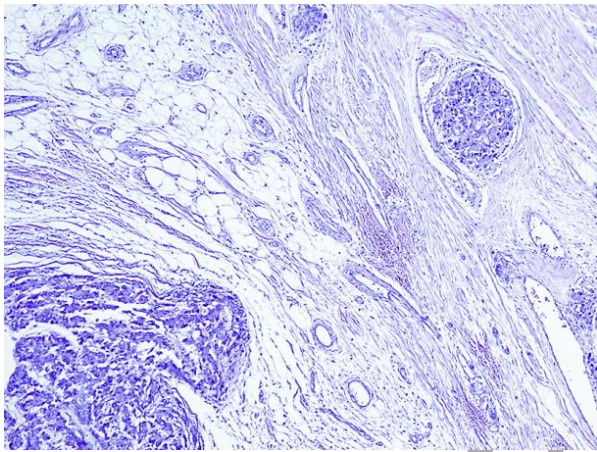


Figure 1. HCC metastases in the skin (HE, 100x)

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

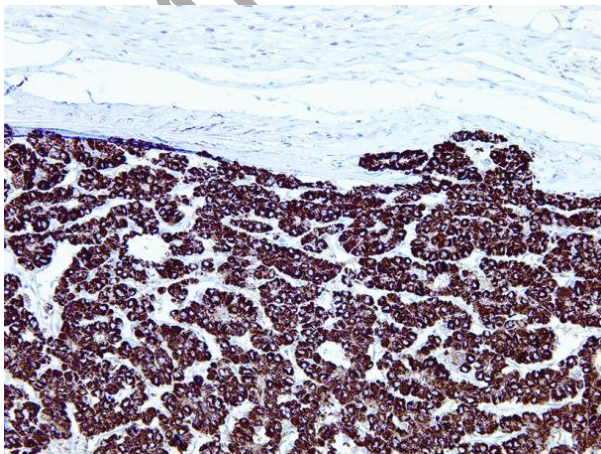


Figure 2. Moderate to strong expression of EMA in the cells of metastatic HCC in the skin (IHC, 40x)

After the performed analysis, a metastasis of hepatocellular carcinoma in the skin was suspected. As part of the examination, a magnetic resonance of the abdomen, bone scintigraphy and a chest CT scan were carried out. After the radiological examinations, a solitary liver tumour, 6cm in diameter, was observed as well as 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 oncology treatment; death occurred 8 months after the hepatocellular carcinoma was first diagnosed.

Case No2

A male patient, aged 61, was referred to a surgeon due to a subcutaneous tumour 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 tumour was noticed, and after the biopsy, the material was sent for histopathologic analysis. The obtained sample contained tumour 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. A stroma of the tumour was scanty. As it was a case of tumour tissue with malignant morphological characteristics, suspected of being a metastatic deposit, an immunohistochemical analysis of the tumour tissue was performed. The immunohistochemical profile of the tumour tissue was: EMA, AE1/AE3, HepPar1 (Figure 3) – positive.

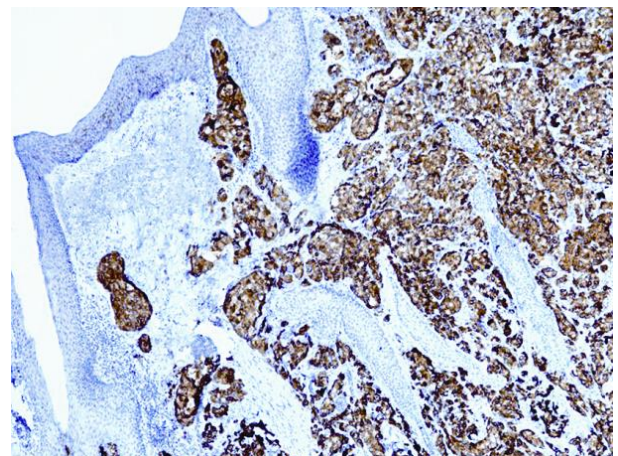


Figure 3. High expression of HepPar1 in the cells of metastatic HCC in the subcutaneous tissue (IHC, 100x)

After a histopathological analysis a subcutaneous metastasis of hepatocellular carcinoma was

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

Case No 3

A patient, 62 years old, was referred to a surgeon due to rapidly growing subcutaneous tumours on the scalp, the parotid region of the neck and the pectoral region. Due to the clinical suspicion that they may be metastatic malignant tumour deposits in the subcutaneous tissue, a resection of the subcutaneous tumour of pectoral region was performed. The material obtained was a whitish, firm node tumour 1,8cm in diameter.

Histopathological analysis revealed tumour 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 tumour tissue were: HepPar1, AE1/AE3, EMA, Vimentin - positive.

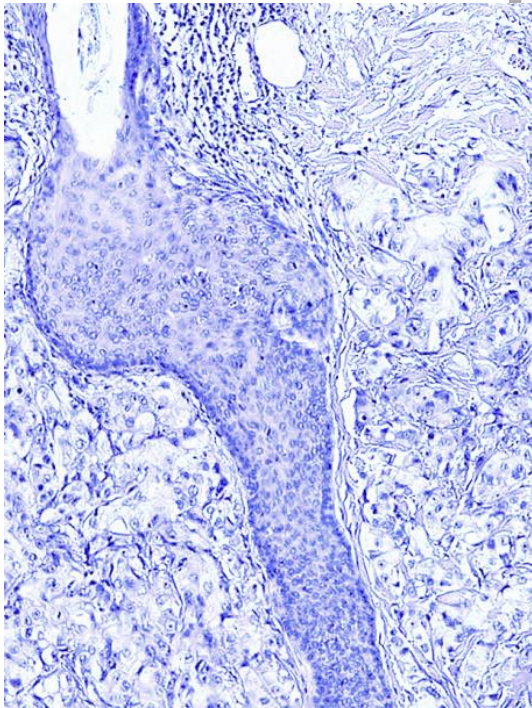


Figure 4. Infiltration of subcutaneous adipose tissue with metastatic HCC (HE, 40x)

After histopathological and immunohistochemical analyses a metastasis of hepatocellular carcinoma

was suspected, and it was later confirmed by radiological and biochemical examinations. AFP value was within normal range. After diagnosis, the patient lived 6 months without oncological therapy.

Histopathological examination

In all three cases, the samples of tumour tissue were fixed in 10% neutral buffered formaldehyde, routinely processed and embedded in paraffin. From the paraffin blocks, cuts of 3-4 μ m 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 60C in a thermostat up to 24 hours. After preparation of the sections in the PT link (Dako, Glostrup, Denmark) (reagent: EnVision Flex Target retrieval solution high pH), further immunohistochemical staining procedure was automated. AUTOIMUNOSTAINER LINK 48 (Dako, Glostrup, Denmark) was used. Dako EnVision Flex System for visualization was used. Primary Dako antibodies, Flex Ready to use were applied and as a chromogen DAB (Diaminobenzidine) was utilised. Contrasting in haematoxylin was done manually (3 to 5 minutes).

Discussion

Hepatocellular carcinoma is the third most common cause of death from all cancers and a leading cause of death in patients with liver cirrhosis (11, 12, 13). It has an aggressive clinical course and it usually spreads through the growth of tumour cells into the lumen of the branches of the portal vein and/or in the lumen of the hepatic veins (10). About 30% to 50% of hepatocellular carcinoma develops extrahepatic metastasis (14), most frequently in the lung, lymph nodes, bones and in the adrenal gland (10, 11). In recent years numerous reports have appeared indicating the 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 maxillary sinus (15), orbit (16), the zygomatic bone (18), the mandible (19), parotid gland (20), larynx (21), in the subcutaneous tissue and the skin (22, 23). Subsequently, the 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 presented with metastases in the skin and subcutaneous tissue. The skin is a relatively unusual place for the presence of metastases and it is believed that less than 10% of all malignant tumours of internal organs metastasize to the skin (1, 24). The metastases of breast cancer, lung cancer and melanoma are most often seen in the skin (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, and rarely on the shoulders and on the trunk (27, 28). Macroscopically, they are presented as nodes with or without ulceration (solitary or multiple), as well as diffuse infiltration (plaque) or as a papule followed by hyperpigmentation (29). In the first case, a metastatic tumour was nodule, localized in the parietal part of the scalp and there was ulceration on the surface of the skin. In the second case, metastatic tumour was presented as diffuse infiltration. Within our third patient, metastases were present as multiple nodules localized subcutaneously in areas of the scalp, parotid region and pectoral region.

The mechanism of metastases occurrence of hepatocellular carcinoma in the skin and soft tissues has not yet been fully clarified. It is believed that the cutaneous metastases occur when the tumours are spread by a haematogenous route or implantation during surgical procedures (22), while the possibility of tumour cells dispersal after percutaneous needle aspiration is highlighted (23, 30). The appearance of cutaneous metastases is indicative that the metastatic disease is 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 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 was noted that in countries with a high risk of developing HCC, this tumour occurs before the age of 20, while in 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

hepatocellular 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 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 correct diagnosis of cutaneous malignant tumours, it is important to distinguish any secondary deposits in the skin from typical skin tumours. 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 often are less differentiated than those in the primary tumour. 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 tumour, 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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**KOŽNE I PODKOŽNE METASTAZE HEPATOCELULARNOG KARCINOMA-
PRIKAZ TRI SLUČAJA**

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Hepatocelularni karcinom (HCC) je treći najčešći uzrok smrti od svih malignih tumora. Metastaze HCC u koži su veoma retke i čine svega 0,8% od svih poznatih kutanih metastaza.

Mi prikazujemo tri slučaja HCC sa metastazama u koži i u podkožnom 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 Hep Par1. U dva slučaja su zabeleženi i povišeni serumski nivoi AFP.

Za dijagnozu ekstrahepatičnih metastaza je važno, 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*