



Metastasis of hepatocellular carcinoma presented as a tumor of the maxillary sinus and retrobulbar tumor

Metastaza hepatocelularnog karcinoma kao tumor u maksilarnom sinusu i retrobulbarnom prostoru

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Abstract

Introduction. Hepatocellular carcinoma (HCC) is the most frequent primary malignant tumor of the liver. It is usually seen in the 6th and 7th decades of life and chronic hepatitis B is the most frequent cause. Extrahepatic metastasis of HCC is an indicator of a poor prognosis and the most common sites are lungs, bones, lymph nodes, kidneys and adrenal glands. We reported a case of isolated metastasis in the right maxilla, which had been found initially, before the tumor in the liver was diagnosed. **Case report.** A 70-year-old man underwent dental surgery of the upper right molar. Prolonged bleeding control was difficult for up to two weeks, so the biopsy was performed. Histopathological analysis revealed a metastatic hepatocellular carcinoma. Computerized tomography (CT) of the abdomen revealed a diffusely heterogeneous liver parenchyma with irregular borders and two foci of mass lesions. There were metastasis in the spleen and also two pathological retroperitoneal lymph nodes were detected, but no ascit, liver cirrhosis, cholestasis or portal vein thrombosis were seen. CT of the orbital and maxillary regions revealed a tumor mass in the right maxillary sinus, spreading to the alveolar sinus, nasal cavity and partially infratemporal space. A tumor mass was in the right orbit as well, infiltrating the surrounding bones and muscles. Clinically, there was proptosis of the right eye accompanied by amaurosis. The treatment started with chemotherapy based on 5-fluorouracil (sorafenib was not available). After three cycles, control CTs showed a stable disease in the liver, but progression in the right maxillary sinus and orbit. Enucleation of the right eye was performed and postoperative radiotherapy was planned. The patient deteriorated rapidly and died, about 6 months after the disease had been diagnosed. **Conclusion.** Extrahepatic metastasis of HCC represents a progressive phase of the disease with poor prognosis, so the main aim of the treatment should be palliation and care of symptoms.

Key words:
carcinoma, hepatocellular; neoplasm metastasis; jaw;
orbit; diagnosis; treatment outcome.

Apstrakt

Uvod. Hepatocelularni karcinom (*hepatocellular carcinoma* – HCC) predstavlja najčešći primarni maligni tumor jetre koji ima agresivan tok sa preživljavanjem od svega nekoliko meseci. Kod oko 80% bolesnika glavni uzročnik HCC je ciroza jetre u kombinaciji sa hroničnim virusnim hepatitisom, pretežno tipa B i C. Prisustvo ekstrahepatičkih metastaza je indikator loše prognoze. Metastaze se najčešće javljaju u plućima, kostima, limfnim čvorovima, bubrezima i nadbubrežnim žlezdama. Predstavili smo bolesnika sa metastazom hepatocelularnog karcinoma u gornjoj vilici i očnoj duplji. **Prikaz bolesnika.** Bolesnik, star 70 godina, bio je podvrgnut ekstrakciji gornjih desnih kutnjaka. Nakon ekstrakcije nastalo je krvarenje koje nije moglo da se zaustavi tokom dve nedelje. Urađena je biopsija okolnog tkiva, a patohistološka dijagnoza potvrdila je da se radi o metastazi hepatocelularnog karcinoma. Na kompjuterizovanoj tomografiji abdomena viđene su hipodenzne fokalne promene u jetri i slezini kao i izmenjeni limfni čvorovi u retroperitonealnom prostoru paraaortalno. Kompjuterizovana tomografija srednjeg masiva lica pokazala je tumor koji u potpunosti ispunjava desni maksilarni sinus, razara alveolarni produžetak i širi se u nosnu šupljinu i infratemporalni prostor. U desnoj očnoj duplji tumor se u potpunosti infiltrisao u spoljašnji pravi mišić pokretač očne jabučice i razarao je spoljašnji zid orbite. Kliničkim pregledom registrovana je protruzija desne očne jabučice. Lečenje je započeto prvom linijom sistemske hemoterapije baziranoj 5-fluorouracila. Nakon tri ciklusa registrovana je stabilizacija bolesti u jetri, ali i dalja progresija u gornjoj vilici i očnoj duplji. Učinjena je enukleacija desnog oka. Planirana zračna terapija predela maksilarnog sinusa i orbite desno nije sprovedena, s obzirom na to da je bolesnik egzistirao. **Zaključak.** Ekstrahepatične metastaze hepatocelularnog karcinoma predstavljaju odmaklu fazu bolesti i indikator su loše prognoze. Iz tih razloga, glavni cilj terapije treba da bude usmeren ka paliativnom lečenju i zbrinjavanju simptoma bolesti.

Ključne reči:
hepatom; neoplazme, metastaze; vilice; orbita;
dijagnoza; lečenje, ishod.

Introduction

Metastatic hepatocellular carcinoma (HCC) is a very aggressive disease with poor prognosis and only a few months' survival¹. It is the most common primary liver cancer². It is usually seen in the sixth and seventh decade of life. About 80% of HCC is caused by cirrhosis combined with chronic viral hepatitis B or C³⁻⁵. Second cause of HCC is alcoholism, with or without viral infection presence⁶. At the moment of diagnosis, about 50% of patients have distant metastases, while the occurrence of extrahepatic metastases indicates a bad prognosis⁷. Most common metastatic sites are lungs, bones, lymph nodes, kidneys and adrenal glands^{4, 5, 8-10}. Rarely, HCC can be manifested as metastatic deposits without primary tumor in liver^{11, 12}. Unlike HCC metastases in the upper jaw which are described more often in the literature¹³⁻¹⁷, the metastases to the maxilla have been seen only in one case¹⁸.

In this paper we presented the patient with hepatocellular carcinoma metastases in the upper jaw and maxillary sinus additionally spreaded to the orbit. It manifested as a prolonged bleeding after tooth extraction.

Case report

A 70-year-old patient underwent surgical removal of upper molars. Two weeks later, biopsy of surrounding tissue due to prolonged bleeding after the applied haemostasis, was performed. Routine histopathological analysis showed malignant metastatic tumor, most probably hepatocellular or renal carcinoma metastasis (Figure 1). In order to reveal the

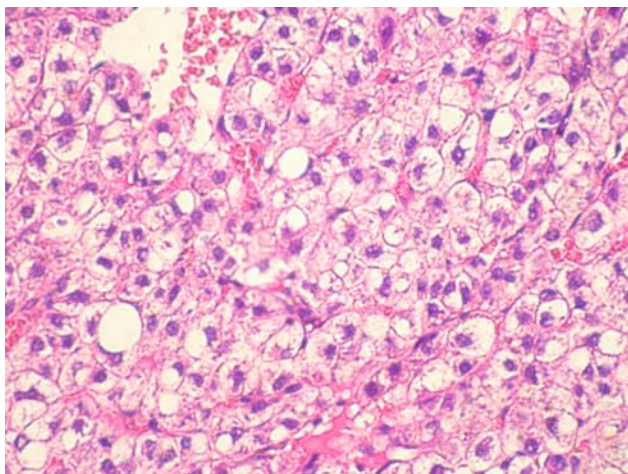


Fig. 1 – Tumor composed of solid sheets of large cells (HE ×100)

metastasis origin, we used additional immunohistochemical staining: HepPar (OCH1E5, 1:25), Vimentin (V9, 1:200), TTF-1 (8G7G3/1, 1:10), CK7 (OV-TL12/30, 1:50), CK20 (Ks20.8, 1:50), made by DAKO and RCC (66.4C2, 1:50) made by Novocastra lab. LSAB+system visualisation. Tumor cells manifested strong immunoreactive staining for HepPar antibody (Figure 2) known as one of the most specific and most sensitive markers for HCC¹⁹. Cells did not show any

immunoreactivity for the other used antibodies: vimentin, TTF-1, CK7, CK20 and RCC antibody.

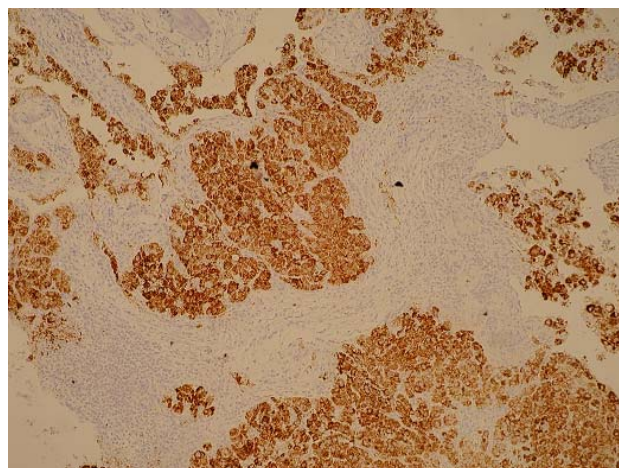


Fig. 2 – Tumor cells reveal diffuse granular staining of cytoplasm (HE ×100)

Abdomen CT showed two hypodense focal changes in the liver (segment VIII), dimensions 22 mm and 30 mm. One hypodense focal change was seen in the spleen, 22 mm diameter, as well as two soft-tissue formations around the aorta, interpreted as abnormal lymph nodes, dimension 21 mm and 44 mm. Nodular formations up to 11 mm were seen in the mesenterium.

CT of the orbital and maxillary regions revealed a tumor mass in the right maxillary sinus, spreading to the alveolar sinus, nasal cavity and partially in the infratemporal space. The tumor mass was also disseminated in the right orbit, infiltrating the surrounding bones and muscles.

Radiography of the lungs and skeletal system was normal.

Laboratory findings before the treatment were: urea 9.0 mmol/L; creatinine 122 µmol/L; total bilirubin 35.4 µmol/L; aspartat-aminotransferase (AST) 86 UI/L; alanin-aminotransferase (ALT) 106 UI/L; alkaline-phosphatase (ALP) 295 UI/L. Alpha-fetoprotein (AFP) was 18309 ng/mL. In blood count, a mild anemia was detected, with hemoglobin level of 102 g/L. All other parameters were within normal ranges.

Clinically, there was proptosis of the right eye, worsening over time, accompanied by amaurosis and a complete loss of vision in the right eye after two months (Figure 3). The patient had a strong pain in the right side of the head, managed by opioid painkillers.

Cirrhosis of the liver and viral hepatitis infection B were not confirmed. The patient was a non-smoker and did not consume alcohol.

Karnofsky Performance Status before the treatment was 80%, but gradually decreased to 60%.

According to the multidisciplinary team (MDT) decision, the treatment started with the first line of systemic chemotherapy based on 5-fluorouracil and leucovorin. Sorafenib was not available. Three cycles were applied, every 28 days. During the chemotherapy, hemoglobin levels



Fig. 3 – Proptosis of the right eye

were gradually decreasing to 88, 76 and 64 g/L, which required blood transfusion several times. After three cycles of chemotherapy, MDT did the evaluation of disease progress. Control CTs showed a stable disease in the liver, but apparent progression in the right maxillary sinus and orbit. Finding in the right eye was also worse with gradual loss of vision. Pain was more intensive and not manageable with morphine analgesics.

The patient was presented to MDT, who indicated enucleation of unfunctional eye with additional radiotherapy of maxillary sinus and right orbit. He was hospitalized in the Clinic for Eye Disease where the planned operation was performed, without any postoperative complications. Histopathology of the enucleated right bulbus revealed deformity caused by spontaneous rupture but no elements of tumor were found. Although all symptomatic therapy was given, the patient's condition was getting worse. Radiotherapy was not performed. The patient died six months after the diagnose had been settled.

Discussion

Hepatocellular carcinoma is a very aggressive disease with a five-year survival in 0.8% men and 4.4% women²⁰. Intrahepatic metastases appear very early and more than 50% of patients have extrahepatic metastases as well¹⁸. A role in metastases development can be recognized in the state of liver parenchyma and the level of liver damage caused by viral hepatitis²¹. Metastases are usually spread by intrahepatic blood and lymphatic vessels or by direct infiltration. Hematogenic spreading means spreading through the hepatic portal vein or vena cava. The most common metastatic sites are: lungs (18.1%–49.2%), lymph nodes (26.5%–41.7%), bones (4.2%–16.3%) and adrenal glands (8.4%–15.4%)^{4, 5, 8–10}.

Treatment of patients with hepatocellular carcinoma depends mostly on the disease stage. When the disease is localized to the liver only, the main therapy option is sur-

gical removal of the tumor. In the locally advanced and metastatic disease, the only choice is systemic chemotherapy. So far, there have been no precise protocols for patients with extrahepatic metastases, but the usage of cytostatics is very often limited by a bad performance status of a patient²².

The patient presented in this paper had metastases in the maxillary sinus spreading to the orbit and nasal cavity. Metastases were also detected in the spleen and paraaortal lymph nodes. Liver cirrhosis and viral hepatitis infection B were not confirmed. Levels of bilirubin, transaminases and alkaline-phosphatase were doubled, while alpha-fetoprotein level was 18.000. The disease was manifested in a metastatic phase so chemotherapy was the treatment of choice. Three cycles of chemotherapy based on 5-fluorouracil were administrated with a final effect of disease progression. Due to spontaneous cornea perforation caused by lagophthalmus and tumor compression, the right bulbar enucleation was performed. Palliative radiotherapy of the maxillary sinus and right orbit was not completed because the patient died. He lived six months after the moment of diagnosis.

While metastases of hepatocellular carcinoma to the mandible have been described in many papers^{13–17}, metastases in the maxilla are very rare¹⁸. Clinical and autopsy findings of these cases revealed two ways of metastatic spreading to the maxillary-facial region. When cancer cells reach the hepatic artery and portal vein, the first metastatic site are lungs. From the lungs, dissemination goes to the maxillary area¹⁸. In other case, if autopsy does not show any metastases in lungs, dissemination to maxillary area is considered to be either by vertebral and azygos vein system or by lymphatic system.

The presented patient had no confirmed lung metastases, which suggested that spreading of cancer cells to the maxillary sinus and the orbit had been by lymphatic or vertebral vein system.

The presence of extrahepatic metastases is an indicator of bad prognosis. In that stage the only treatment is chemotherapy. Due to very aggressive nature of disease with rapid deterioration of performance status, it is very important to make a good assessment of treatment benefit and potential risks. The main aim of treatment should be palliation and symptom care.

Conclusion

In this paper we described an unusual hepatocellular carcinoma metastasis, as bleeding tumor in the maxillary sinus spreading to the orbit. In such case, it is quite possible to overlook the real origin of prolonged bleeding in a patient with previous intervention on molars. Due to that, it is important to make a proper diagnosis and find the cause of every unusual complication, even if they appear after small interventions.

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