Extrahepatic Metastases of Hepatocellular Carcinoma: a Case Report

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Introduction

Hepatocellular carcinoma (HCC) is a malignancy of worldwide significance and has become increasingly important in economically developed regions. HCC is the most common primary liver malignancy, the sixth most common cancer, and the third most common cause of cancer related deaths worldwide (1). HCC represents approximately 85% of all primary liver cancers (2). In Western countries, HCV infection and alcoholic cirrhosis are the principal risk factors for HCC. The incidence increases with age, the median age group of HCC is between the fifth and sixth decades. Overall, HCC has a very poor prognosis, with a 5-year survival rates of 5%.

Case Presentation

We report the case of a 70-year old Caucasian man, without family history for cancer, who was referred to The Oncology Institute “Prof. Dr. Ion Chiricuta” in June 2014 for the management of a tumor mass present on the anterior chest wall. The patient comorbidities are chronic viral C hepatitis, type 2 diabetes and Budd-Chiari syndrome.

When he first came in our service, he had a good clinical condition, with a PS=1 and without subjective complaints, except loss of appetite. The clinical examination was normal, except the presence of a tumor mass on the right anterior chest wall, subcutaneous, with a diameter of 8 cm, rigid, painless on palpation and without mobility from underlying plans.

The initial workup included a chest X-ray which showed a 7 cm. diameter opacity, in the right middle lung field, in the postero-anterior incidence (fig.1). In the latero-lateral incidence the opacity is localized in the anterior thoracic region (fig. 2).

A thoracic, abdominal and pelvic computed tomography (CT) exam was performed. The examination showed a hypodense tumor localised on the anterior chest wall, under the muscular plan, of 65/70/95 mm, which determines rib lysis (anterior C2, C3) and invades the pleura (fig. 3).

Also, in the lung parenchyma there where nodular hypodense lesions, with low intake, of 7 to 8 mm., localised in the left apical field, with a CT aspect suggestive for secondary lesions; thrombosis of inferior cave vein and hepatic vein- Budd-Chiari syndrome. In the VIII and VI liver segment: hypodense lesions, 9 to 27 mm. diameter,
At that time, we concluded that the patient had a lung tumor with lung and liver metastases. We performed a biopsy from the chest wall mass. The histopathological exam and the immunohistochemistry (IHC) profile showed: CK AE1/AE3 negative, CK7 negative, CK20 negative, hepatocytes positive, CD99 positive, S100 positive in isolated cell, p63 negative. The histology and IHC profile were compatible with a parietal metastasis of a hepatocellular carcinoma.

Biologically, the patient had increased values of liver transaminases: ALAT=54 U/L and ASAT=122 U/L, an elevated LDH=268 U/L, and AFP=23906 ng/mL.

We concluded that the patient's diagnosis was hepatocellular carcinoma cT2N0M1 (lung and chest wall metastases) stage IVB disease. Chemotherapy with FOLFOX4 was initiated, until the National Health Insurance House approval for Sorafenib. So far 2 cycles of FOLFOX4 were administered with stable disease.

**Discussion**

Early detection, surgical removal of the lesion, transcatheter arterial chemoembolization (TACE), transcatheter arterial radioembolization (TARE) or chemotherapy are effective in managing the disease. However, the disease is contained within the liver in only 20% of cases. HCC invades the portal vein in 35% of cases, hepatic vein in 15%, contiguous abdominal organs in 15%, and cave vein and right atrium in 5%. HCC metastases appears into the lung in 35% of cases, abdominal lymph nodes in 20%, thoracic or cervical lymph nodes in 5% and kidney or adrenal gland in 5% (3).

The incidence of bone metastases is 13-16% and it is well described (4,5). It infrequently appears as the first manifestation. The most common sites of skeletal involvement are vertebra, pelvis, ribs, humerus and sternum (5). Unlike these reported cases, our patient presented with anterior chest wall mass and lytic lesion in the 2th and 3th ribs. Only a few other reports to our knowledge have patients presenting in a similar way. (6,7,8,9).

Metastasis of HCC occurs frequently by intrahepatic blood vessels, lymphatic permeation or direct infiltration and it is difficult to show exactly how tumor cells spreads to bones in its early stages (9). Metastatic spread occurs through the pulmonary circulation or the vertebral venous plexus because bone metastasis of HCC is seen frequently in patients without lung metastasis (10). But in this case, our patient presented with chest wall mass and pulmonary metastases, and this is a feature of this case.

Metastases in hepatocellular carcinoma is a significant clinical problem and they usually indicate incurable disease with a poor prognosis. Lung metastases are generally associated with a shorter median survival. Isolated lung metastases are rare, most of the patients present with multiple lung metastases and requires a systemic treatment such as
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Chemotherapy or biologic therapy. Metastatic hepatocellular carcinoma is by definition an advanced and systemic disease, and the standard approach is to obtain disease control with effective systemic therapies.

The patient started FOLFOX4 chemotherapy regimen for 2 cycles, and he will be treated with sorafenib after that. A randomized phase III study from China demonstrated the utility of FOLOFOX4 chemotherapy versus doxorubicin, in advanced cases. Median OS with FOLFOX4 (N = 184) was 6.4 months vs. 4.9 months with doxorubicin (n = 187) (p = 0.0859 using a stratified log-rank test; HR 0.797 [0.625, 1.017]). Median TTP with FOLFOX4 was 2.9 months vs. 1.8 months with doxorubicin (p < 0.0001; HR 0.620 [0.489, 0.787]) (11). There are some phase II studies which demonstrate a good tolerance for GEMOX and Bevacizumab therapy and the median overall survival was 9.6 months (95% CI, 8.0 months to not available) and median progression-free survival (PFS) was 5.3 months (95% CI, 3.7 to 8.7 months) (12,13).

Advanced hepatocellular carcinoma with good function of the liver or with intermediary risk who progressed after TACE, benefits, as antiangiogenetic therapy, from sorafenib. The trials demonstrated the efficacy and safety of sorafenib in patients with advanced (unresectable or metastatic) hepatocellular carcinoma. In a phase III randomised, double-blind, placebo-controlled trial with sorafenib in advanced HHC the results showed median overall survival was 6.5 months (95% CI 5.56-7.56) in patients treated with sorafenib, compared with 4.2 months (3.75-5.46) in those who received placebo (hazard ratio [HR] 0.68 [95% CI 0.50-0.93]; p=0.014). Median TTP was 2.8 months (2.63-3.58) in the sorafenib group compared with 1.4 months (1.35-1.55) in the placebo group (HR 0.57 [0.42-0.79]; p=0.0005) (14).

**CONCLUSION**

The lung, abdominal lymph nodes, and bone are the three most common sites of extrahepatic HHC. The detection of extrahepatic HHC is important for patients with HHC to receive the appropriate therapy, which de-termines patient survival.

**REFERENCES**