

Case report**Metastasis of hepatocellular carcinoma in the orbit as first manifestation of extrahepatic spread- A case report and review of the literature****Iliana Mani¹, Despina Gkeka², Florentia Athanasaki¹, Krystallia Dimitriou², Theodoros Alexopoulos¹, Evangelia-Anna Spiteri⁴, Alexandra Alexopoulou¹**¹2nd Department of Internal Medicine, Medical School, National & Kapodistrian University of Athens, Hippokration General Hospital, Athens, Greece.²Department of Oncology, Medical School, National & Kapodistrian University of Athens, Hippokration General Hospital, Athens, Greece.³Department of Pathology, Evangelismos General Hospital of Athens, Athens, Greece.**Abstract.**

Hepatocellular carcinoma (HCC) is the most frequent primary liver malignancy. Half of the patients with HCC present metastases, most commonly in the lungs, bones, and lymph nodes. Despite all current treatment options, life expectancy remains low, especially for patients with metastatic disease. A case with an uncommon metastatic HCC location in the orbital cavity is herein presented and a systematic review of another 36 cases with the same metastatic site is performed.

Key words: Hepatocellular carcinoma; orbital metastasis; review of the literature

Introduction

Primary liver cancer is one of the most common malignancies globally, being the sixth cause of cancer and third in cancer-related mortality [1]. Its incidence is expected to rise even further by 2040 [1]. Hepatocellular carcinoma (HCC) consists of the 75-85% of all primary liver malignant neoplasms. Liver cirrhosis of any cause is the most important risk factor for HCC development [2].

Extrahepatic metastatic HCC was estimated at 15-50% [3-7] with the most common sites being the lungs (47-55%), lymph nodes (45-53%), bones (28-37%) and adrenal glands (11-12%) [8]. Less frequently, HCC metastases are found in the peritoneal cavity, brain, spleen, pancreas, gall bladder, diaphragm, skin, and digestive track [9]. Extrahepatic spread increases patient's Barcelona Clinic Liver Cancer (BCLC) stage (C or D) and shorten survival [10]. However, intrahepatic disease and performance status and not extrahepatic metastasis were significantly associated with prognosis [11].

Orbital metastases are scarce and correspond to only 3-7% of orbital masses [12-13]. The most common symptoms include double vision,

eye protrusion and vision impairment [14]. Remarkably, eye complications develop before identifying the primary malignancy. Lung and breast carcinomas are most associated with metastatic orbital foci [14]. In large cohorts with orbital metastatic disease, none was attributed to HCC [15].

We present the case of a patient with HCC and a single metastasis at the orbital cavity, manifested as sudden orbital hematoma with concomitant visual impairment. We also review the existing literature about histologically proven orbital metastasis of HCC including patients' demographic characteristics, histological findings, and data about survival when available.

Method of Literature Search

We searched in Pubmed and Scopus using the terms HCC and ocular metastases or orbit metastases. Only articles in English language were included. No time limit was applied. Reference lists of the included articles were further scanned for additional references.

Case presentation

A 54-old woman, presented with a 15-year history of untreated chronic hepatitis C. Ultrasound revealed the presence of cirrhosis and four liver nodules with a maximum diameter of 5.5 cm consistent with HCC. Magnetic resonance imaging (MRI) confirmed the diagnosis of multifocal HCC. A-fetoprotein (AFP) was measured at 200 ng/ml. According to BCLC staging system, HCC was classified as stage B [10].

For the next four months following diagnosis, she has been receiving two transarterial chemoembolization (TACE) sessions. One month after the last TACE session, MRI revealed stable disease according to the modified-Recist criteria for HCC [16]. AFP levels dropped to 25 ng/ml but the patient experienced sudden pain in the left eye with spontaneous hematoma locally, ocular proptosis and vision impairment.

MRI revealed the presence of an intraocular mass with concomitant infiltration of the left frontal bone. Histological examination revealed

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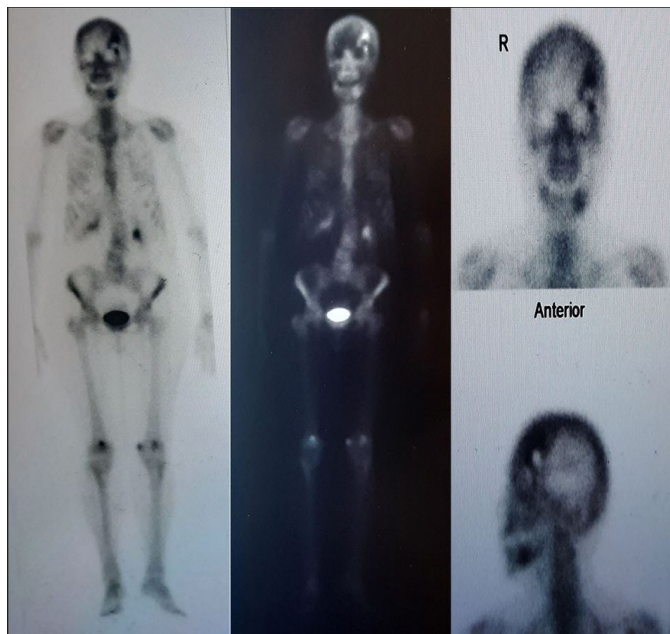


Figure 1: Bone scintigraphy revealing a sole bone metastasis in the left frontal bone, above the left orbital cavity.

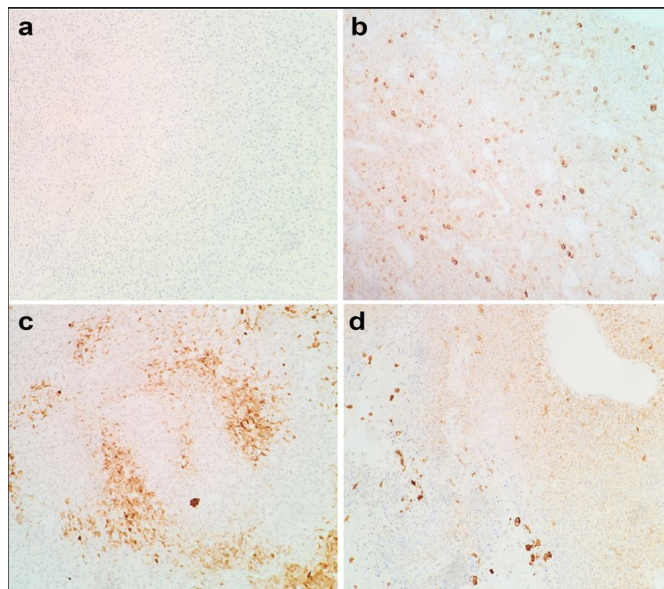


Figure 2: Histopathological examination of the intraorbital mass: a) Negative stain for Hepatocyte paraffin 1; b) Positive stain for Glypican-3; c) Positive stain for Heat Shock Protein-70; d) Positive stain for Glutamine synthetase.

Table 1: Clinical and demographic characteristics of 36 cases with a hepatocellular carcinoma metastasis in the orbit (References 27, 28 and 34 include 2, 3 and 6 cases respectively).

Demographics and Characteristics of the disease	Number of patients (%)	References
Etiology of liver disease		
Chronic hepatitis B	10 (27.8%)	12,23,26-27,31-33,38-40
Chronic hepatitis C	14 (38.9%)	17,22,24,28-30,34
Alcoholic liver disease	5 (13.9%)	13,18,27,35,41
Unknown	7 (19.4%)	19-21,25,36-37,42
Characteristics of orbital metastasis		
Location		
Left eye	20 (55.6%)	12-13,21-22,27-28,32,34-36,38-42
Right eye	15 (41.7%)	17-20,24-26,28-31,33-34,37
Both eyes	1 (2.8%)	23
Symptoms		
Proptosis	23 (63.9%)	12,17-21,25-27,29-30,32-34,36-39, 41
Visual impairment	4 (11.1%)	13,28,31,35
Palpable mass	3 (8.3%)	28,40
Diplopia	2 (5.6%)	22,42
Periorbital edema	2 (5.6%)	24,27
Blepharoptosis	2 (5.6%)	23,34
History of HCC		
First manifestation of HCC	24 (66.7%)	12-13,18-21,23,25-29,30-31,33-37,39
Already diagnosed HCC	11 (30.6%)	17,22,24,28,32,34,38,40-41
Missing information	1 (2.8%)	42
Other metastatic lesions		
Sole orbital metastasis	10 (27.8%)	12,17,19,23-25,29,35-36,38
Extraorbital metastases	10 (27.8%)	13,18,20,22,26-27,32,37,40
Missing information	16 (44.4%)	21,28,30-31,33-34,39,41-42
Treatment		
Radiation	9 (25%)	13,17-18,27-28,30,32
Surgical resection	4 (11.1%)	22,24,38,41
Systemic therapy	2 (5.6%)	33,39
Radiation and systemic therapy	1 (2.8%)	35
No therapy	8 (22.2%)	12,20-21,25-27,31,36
Other	3 (8.3%)	29,37,40
Missing information	9 (25%)	19,23,34,42

invasion with low differentiation HCC, a diagnosis based on the positive staining for glutamine synthetase, glypican-3 and heat-shock protein 70 (Fig. 1), while common markers of hepatocellular differentiation, namely hepatocyte paraffine-1 and AFP, were negative. No further metastatic lesions were revealed in imaging studies.

Treatment with atezolizumab and bevacizumab with concomitant radiation of the ocular lesion was administered. After three months, disease progressed with evidence of ascites, bone and lung metastases. Treatment changed to cabozantinib without any improvement. She died 6 months after diagnosis of the ocular metastasis.

Discussion

We present a patient with rare orbital metastasis as the first extrahepatic manifestation of HCC. Only 36 cases of ocular metastatic disease related to HCC are reported since 1981 [12-13, 17-42]. Most patients were male (77.1%), with a median age of 61 (range 54-70) years. The commonest causes were chronic hepatitis C and B. Median duration of symptoms before diagnosis was 6 (4-8) weeks with ocular prolapse being the dominant symptom, followed by visual impairment and palpable mass (8.3%). The left eye was more frequently affected. In the 68.6% of cases, orbital metastasis was the first manifestation of HCC. In the 27.8%, orbital was the only metastatic lesion identified (Table 1). Immunohistochemical characteristics were provided in about half of the cases [12,17,19-20,22-24,28-29,31-33,37,41]. AFP (6/8), CEA (6/10) and hepatocyte Paraffin 1 (6/6) were the most expressed biomarkers. Cytokeratin AE1/AE3 staining was negative in most cases (7/9) for which it was available. In the present case, histologic confirmation of the diagnosis was made using the highly specific immunohistochemical combination of glypican-3, heat shock protein 70 and glutamine synthetase since the most frequently HCC-associated stains were negative [43].

As far as treatment is concerned, the 25% of patients underwent radiation treatment, two received systemic treatment and only one was treated with a combination of both. Twenty-three patients were diagnosed after 2007, when sorafenib emerged as the first systematic treatment modality shown to improve overall survival in HCC. However, since 2007, only one patient in the literature received systemic treatment. In total, in eight (22.2%) no systemic treatment was administered (Table 1). Survival data were available for about half of the cases [17,20-23,26-28,31,33,35-37,40]. The median survival was 4.5 (2-10.7) months.

Regarding the mechanisms of orbital metastases in HCC, a haematogenous spread of the tumor cells may be involved. They may pass through the vena cava, go through pulmonary field to the heart and reach orbital region through the arterial systemic circulation. Another possible spread mechanism is reaching the head through the vertebral venous plexus of Batson after bypassing the lungs [13]. It is unclear if TACE contributed to the aggressive features of the disease. It has been proposed that TACE – induced liver hypoxia is associated with neo-vascularization as well as with activation of proteins that either stimulate progenitor liver cells or confer to the impairment of the extracellular matrix, thus, increasing the metastatic potential of HCC [44].

In conclusion, orbital metastasis is an uncommon site of extrahepatic HCC. Diagnosis can be challenging, especially when immunohisto-

chemical markers of hepatocellular differentiation are negative. Metastatic hepatocellular carcinoma is associated with poor prognosis for most patients with the currently available treatment approaches.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

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