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Hepatocellular Carcinoma Metastatic to the Orbit: A Case Report

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Hepatocellular carcinoma rarely metastasizes to the orbit. We report on a 72-year-old man with a past history of resection for hepatocellular carcinoma and recurrent HCC, who presented with diplopia and left painful proptosis. Head scans revealed a large and irregular mass in the left orbit that caused destruction of the orbital bone superiorly and posterolaterally. A biopsy specimens of the orbital tumor showed features of metastatic foci of hepatocellular carcinoma. The tumor was surgically excised and histological findings revealed moderately differentiated hepatocellular carcinoma, resembling hepatocytes with a tendency to form trabeculae. Immunohistochemically, the tumor cells showed positive reaction against low-molecular-weight keratin and α-fetoprotein. There have been only 12 previous cases of hepatocellular carcinoma metastatic to the orbit cited in the literature. We presented here a rare case of hepatocellular carcinoma metastatic to the orbit.

Key words: hepatocellular carcinoma, orbit, metastasis

INTRODUCTION

Although autopsies of patients who died of hepatocellular carcinoma (HCC) have revealed evidence of metastases in 50-75% of cases, the extrahepatic manifestation of clinically diagnosed cases is relatively uncommon [1]. Usually, metastasis from HCC occurs, in descending order of frequency, to the lung at 41.4-51.6%, lymph nodes at 26.7-37.9%, peritoneum at 4.0-10.9%, gallbladder at 4.3-11.6%, adrenal glands at 5.8-10.9% and bone at 4.8-8.8% [2]. Metastasis to the orbit is rare. Ferry and Font, in a review of 227 cases of metastatic carcinoma in the eye and orbit, reported no cases of orbital metastasis from HCC [3]. We present herein a case of this metastatic tumor, and the relevant literature is also reviewed.

CASE REPORT

A 72-year-old man presented with diplopia on upward gaze and consulted an ophthalmologist, whose clinical diagnosis was a left intraorbital tumor, in March 2002. Ten years ago, he underwent partial resection for HCC in the S_7 subsegment and received transarterial embolization (TAE) therapy for recurrent HCC in both lobes of the liver at our hospital. Findings from an incisional biopsy of the orbital mass revealed it to be metastasis from HCC. He was admitted to our hospital for detailed ophthalmologic examination and treatment in April 2002. On physical examination, he was moderately obese with left proptosis and inferior displacement of the eye globe. Apart from decreased visual acuity, and no other cranial nerve palsies were detected. His abdomen was soft and flat, and his liver edge was not palpable. The results of laboratory tests on admission were as follows: white blood cell count, $5.5 \times 10^3/mm^3$; red blood cell count, $357 \times 10^4/mm^3$; hemoglobin, 11.8 g/dl; platelet count, $18.1 \times 10^4/mm^3$; asparate aminotransferase (AST), 160 U/l; alanine aminotranferase (ALT), 127 U/l; alkaline phosphatase, 358 U/l; albumin, 3.6 g/dl; total bilirubin, 0.3 mg/dl. Coagulation tests were all within normal limits. However his serum α-fetoprotein (AFP) at 31511.5 ng/ml was remarkably elevated. Hepatitis B surface antigen was negative and hepatitis C antibody was positive. Skull x-ray and orbital films showed destruction of the left orbital roof. Also, head computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated an 55×30 mm mass in its maximal horizontal diameter involoving the superior and posterolateral wall of left orbit with destruction of the orbital roof and extension into the left cranial fossa (Fig. 1). Arteriograms revealed extensive vascular supply with contributions by the maxillary and ophthalmic arteries, and abdominal CT showed multiple nodules of HCC in both hepatic lobes. Furthermore, a bone scintiscan disclosed evidence of the metastasis to the right femur 3th lumber vertebrae. His chest x-rays showed no evidence of pulmonary metastasis. The tumor was excised through an extradural, left frontotemporal craniotomy in May 2002. The affected bone was then extensively replaced by a soft whitish tumor. The tumor did not invade into the subdural space. Microscopic examination showed a diffuse infiltrate of atypical polygonal cells which contained hyperchromatic nuclei in the esoinophilic cytoplasm. The growth pattern was trabecular with the occasional formation of well-defined lumina (Fig. 2a, b). Immunohistochemically, the tumor cells positively stained for AFP and low-molecular-weight cytokeratin (CAM5.2) (Fig. 3), but showed negative immunoreactivity against polyclonal CEA, chromogranin A, NSE, S-100 (Table 1). These features were consistent with metastatic HCC with moderate differentiation. Postoperatively, he underwent an additional TAE therapy for the residual tumor in the left anterior cranial

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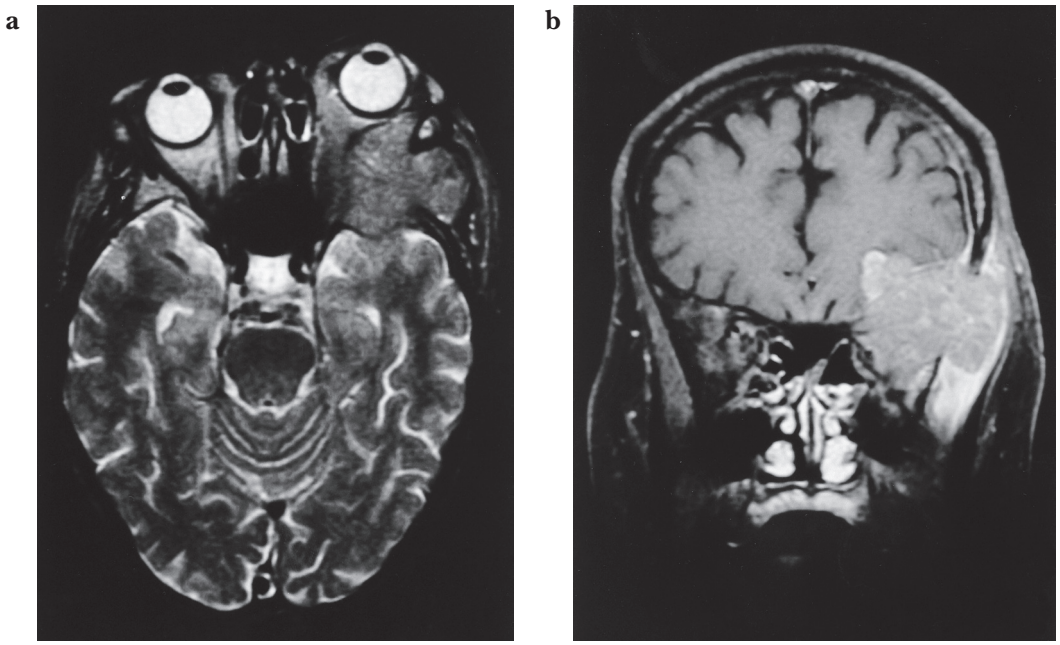

Fig. 1 T1 weighted cranial MRI showed an 55×30 mm mass in its maximal horizontal diameter involoving the superior and posterolateral left orbital wall with destruction of the orbital roof and extension into the left cranial fossa. (**a**: axial, **b**: coronal)

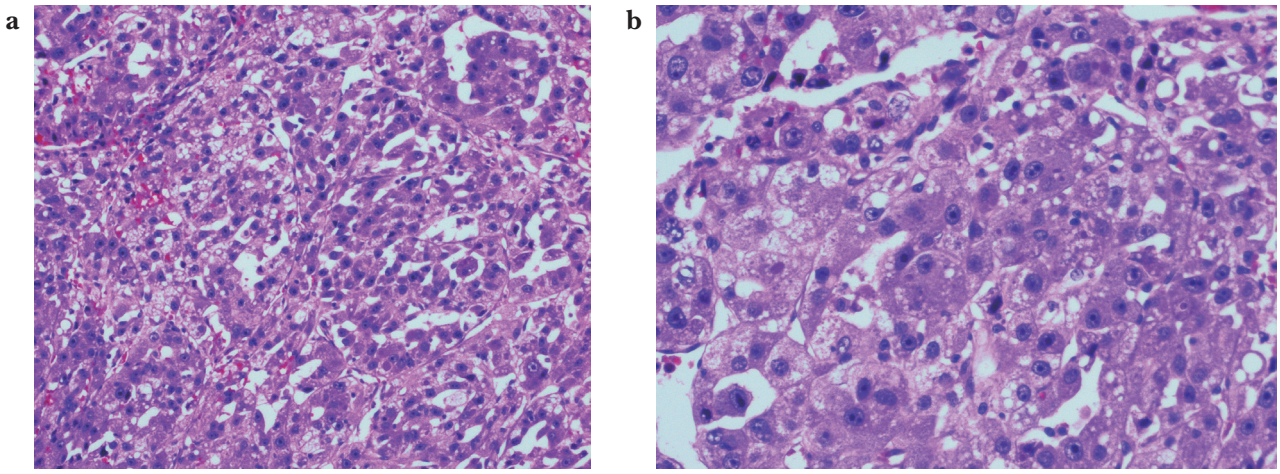

Fig. 2 Histopathological examination of the orbital tumor revealed diffuse infiltrate of atypical polygonal cells which contained hyperchromatic nuclei in the esoinophilic cytoplasm. The growth pattern was trabecular with the occasional formation of well-defined lumina (H&E, **a**: ×40, **b**: ×100).

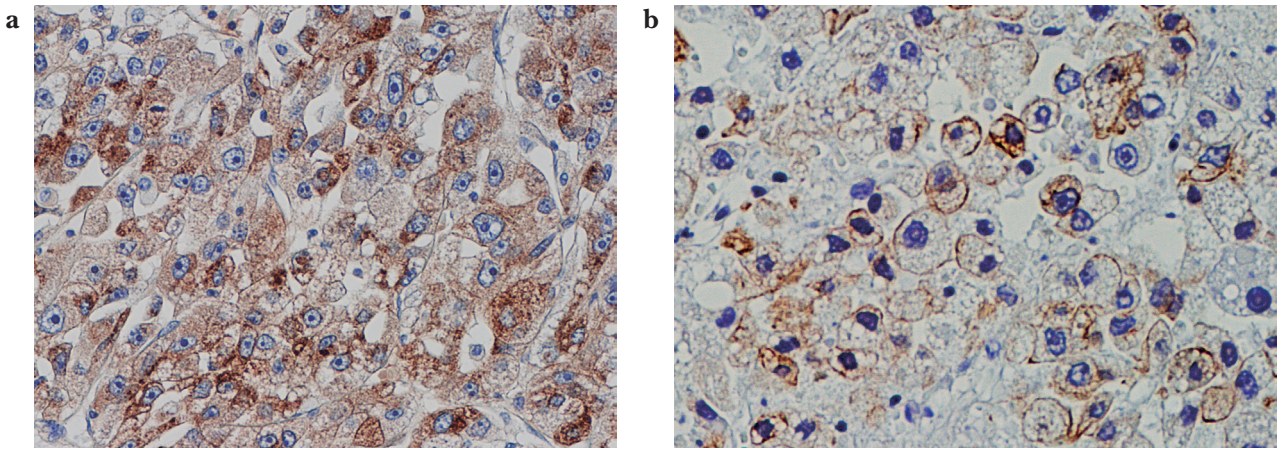

Fig. 3 The orbital tumor was positive by immunoperoxidase staining for (**a**) AFP, and (**b**) CAM 5.2 antigen (×100).

Table 1 Results of immunohistochemical staining for the left orbital mass

Stain Performed	Result
Low-molecular -weight keratin (CAM 5.2)	Positive
High-molecular -weight keratin (AE 3)	Negative
Polyclonal carcinoembryonic antigen	Negative
α-Fetoprotein	Strongly positive
α_1-antitrypsin	Negative
S100 protein	Negative
Chromogranin	Negative
Neuronal specific enolase	Negative

Table 2 Previously reported cases of HCC metastatic to the orbit

	Patient data			Metastasis in the orbit				After diagnosis of the metastasis	
No.	First author	Age	Gender	Symptom	Location	Verification of diagnosis	Interval after diagnosis of HCC	Treatment	Outcome
1	Lubin	69	M	Proptosis	Right orbit	Biopsy	?	Rad	Alive ?
2	Zubler	64	M	Proptosis, ophthalmoplegia	Left orbit	Biopsy	-	Rad	Died 4m
3	Goto	56	M	Proptosis, pain, decreasing vision	Right orbit	Incisional biopsy	-	Chemo + Rad	Died 8m
4	Wakisada	58	M	Diplopia, proptosis, ptosis	Left orbit	Biopsy	-	Operation	Died 11m
5	Schwab	19	M	Proptosis	Left orbit	Biopsy	-	None	Died 1m
6	Tranfa	85	M	Ptosis, pain, decreasing vision	Right orbit	Biopsy	-	?	?
7	Loo	71	F	Proptosis, pain, decreasing vision	Right orbit	Biopsy	?	Rad	?
8	Kami	60	M	Proptosis, headache	Left orbit	Biopsy	-	None	Died 3m
9	Phanthumcinda	29	F	Painful ophthalmoplegia	Left orbit	Biopsy	-	?	?
10	Front	79	F	Proptosis, ptosis, decreasing vision	Right orbit	Incisional biopsy	-	Rad	Alive 3y
11	Scolyer	78	M	Periorbital swelling	Right orbit	Needle biopsy	2m	Operation	?
12	Kim	56	F	Displacement	Left orbit	Biopsy	-	None	Died 2m
13	Our case	72	M	Diplopia, pain, proptosis	Left orbit	Inscisional biopsy	10y	Operation	Died 4m

M, male ; F, female ; -, no interval ; ?, unknown (not described) ; y, year ; m, month ; chemo, chemotherapy ; rad, radiotherapy

fossa. Thereafter, his condition was stable for 2 months until he developed jaundice and ascites. Abdominal ultrasonography detected multiple nodules in the liver with tumor thrombi in the portal veins. His serum AFP level was rapidly elevated to 62086.8 ng/ml and he began to deteriorate day-by-day. He died of liver failure 4 months after his first manifestation of the orbital tumor. An autopsy was not performed.

DISCUSSION

The incidence of orbital metastasis in the literature is described from 3 to 9% of all orbital tumors [4]. The most common primary sites accounting for the vast majority of orbital metastases are the breast and the lung, followed by genitourinary and gastrointestinal primaries [3]. Clinically diagnosed cases of HCC to the orbit are rare. As far as we know, only 12 cases of HCC metastatic to the orbit have been reported [5-16]. Table 2 describes these cases including ours.

A metastatic tumor is diagnosed based on histological findings which show a typical trabecular pattern of growth associated with plump polygonal cells with centrally placed nuclei, cells separated by sinusoidal stroma, nuclear pseudoinclusions, eosinophilic cyto-

plasmic globules, and bile secretion. However, because of the extreme lack of differentiation, sometimes it is difficult to diagnose the orbital tumor to be of hepatic origin solely. Therefore the diagnosis can be aided by performing immunohistochemical staining through the use of a panel of antibodies comprising CAM 5.2, which recognizes keratin 8, AE1, which recognizes keratins 10, 14, 15, 16, and 19, and polyclonal CEA and AFP. CAM 5.2 vividly outlines the cell membranes of neoplastic hepatic cells, which are negative for monoclonal AE1 antibody. Polyclonal CEA marker demonstrates the presence of bile canalicular structures, a feature highly specific for HCC. AFP has been reported to be positive in up to 70 to 90% of HCC [17]. In our case, the histological and immunohistochemical features of the orbital tumor were considered compatible with those of HCC.

The clinical manifestations of metastatic carcinoma are usually characterized by diplopia, proptosis, ptosis, acquired strabismus, conjunctival hyperemia, pain and decreased vision, periorbital swelling and ophthalmoplegia, as documented in patients with orbital metastasis from HCC [3]. When the tumor infiltrates the choroids, blured vision is the predominant effect. Diplopia can be the first symptom and may be minimal. Proptosis and bulb divergence occur when large tumors are present. Generally, metastases in the head and neck regions from HCC become quickly symptomatic, although the primary tumor is often asymptomatic until an advanced stage. In our review of the literature, 9 of 11 patients with orbital metastasis from HCC had initial symptoms caused by the metastatic lesions.

The mechanism of metastasis to the orbit is difficult to determine. A hematogenous route has been noted to be characteristic for primary neoplasms of the abdomen [18], and HCC also may be followed by a hematogenous distribution with metastasis to other organs. Tumor cells may circulate through the vena cava, beyond the pulmonary filters to the heart, finally being distributed to the orbital region throughout the arterial systemic circulation. However, others reported that tumor cells in the majority of cases reach the head and neck by bypassing the lungs, possibly through the vertebral venous plexus of Baston [19]. In the present case, due to the cascading fashion of the defect from the pulmonary metastasis and the evidence of vertebral metatastasis, we also speculate that the vertebral venous plexus may contribute to this metastasis. Furthermore, concerning the establishment of orbital metastasis, there are two possibilities, one is direct metastasis to the orbit, and the other is metastasis/infiltration to the orbit secondary to metastasis to the cranium constituting the orbit. In our patient, cranial destruction was marked, suggesting growth to the orbit secondary to cranial metastasis as was observed in the case reported by the case reported by Wakisaka [8] *et al.*

The metastasis has been treated by surgery, radiotherapy, and chemotherapy. Three of 11 patients including ours had theirs surgically excised. Usually, the metastases are a late event in the progression of HCC, and therefore the prognosis after the assessment of these lesions is generally poor. In our review of the literature, 2 cases including ours may probably have resulted from prolonged survival of the patient when treated with modern modalities and 7 of 8 patients for whom follow-up data was available died within one year because of the rapid growth of the primary lesion and multiple metastases. In recent years, the clinical significance of diagnosing and treating extrahepatic metastasis has increased in direct proportion to the expanding role of chemotherapy and radiation in the treatment of metastatic disease. Although the orbital metastasis is rare, physicians should be aware of its clinical and prognostic implications and thus make efforts to palliate the patient's symptoms as far as possible.

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