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Bilateral orbital metastasis as an initial presentation of hepatocellular carcinoma

Kay Thi Myint[1], Ko Ko Thant[2], Moe Thazin[3]
[1]Faculty of Medicine, SEGi University, Sibu Clinical Campus, Sarawak, Malaysia; [2]Department of Ophthalmology (Retired), University of Medicine 2, Yangon, Myanmar; [3]Department of Ophthalmology, Hlaing Tha Yar General Hospital, Yangon, Myanmar

Abstract

Purpose: *To describe a case of biopsy-confirmed bilateral orbital metastasis of previously undiagnosed hepatocellular carcinoma, presenting with bilateral proptosis.*

Case description: *A 57-year-old man presented with painless bilateral proptosis over 2 months. At presentation, the best-corrected visual acuity was 20/60 in the right eye and 20/20 in the left eye. Ocular examination revealed bilateral asymmetrical non-axial proptosis with Hertel exophthalmometer reading of 24 mm in the right eye and 22 mm in the left eye. There was mild inferior displacement in both eyes. Apart from mild exposure keratopathy in the right eye, both anterior and posterior segment examinations were not remarkable. Orbital computerized tomography (CT) scan showed soft tissue masses in the superotemporal quadrants of both orbits associated with lytic bone lesions. An orbital biopsy confirmed that it was metastatic hepatocellular carcinoma (HCC). Ultrasound abdomen revealed multifocal HCC with underlying cirrhosis. We planned for further investigations such as hepatitis serology, alfa-fetoprotein, and CT abdomen, but he refused to proceed with investigations and treatment.*

Conclusion: *Orbital metastasis, more so as a bilateral involvement, is a rare phenomenon. It may present as an initial manifestation of undiagnosed systemic cancer. Orbital metastasis should be considered when diagnosing patients with bilateral proptosis, and orbital biopsy is crucial for histopathological diagnosis.*

Keywords*: bilateral proptosis, hepatocellular carcinoma, orbital metastasis, ocular oncology, ocular pathology*

Correspondence: Dr. Kay Thi Myint, Faculty of Medicine, SEGi University, Sibu Clinical Campus, Sarawak, Malaysia.
E-mail: kaythimyint.eye@gmail.com

Introduction

The orbit is an unusual site for cancer metastasis. Metastatic orbital tumors are rare conditions that account for 3–7% of all orbital neoplasms. It occurs in 2–3% of patients with systemic cancers.[1] It is more commonly associated with carcinomas of breast, lung, and prostate, and less commonly with kidney, skin, and gastrointestinal tract. Most cases present with unilateral involvement.

Hepatocellular carcinoma (HCC) is a primary malignant tumor derived from hepatocytes. It accounts for 80% of all liver cancers. It is one of the cancers with the highest mortality rates globally and the third most common cause of cancer-related deaths in the Asia-Pacific region.[2] In East and Southeast Asia, it is associated with the highest incidence and mortality among both sexes.[3] Men have a higher incidence, and it is more common in those aged 65 years and above.[2] The most common and well-known risk factor is chronic infection with hepatitis B and C viruses. Other risk factors include obesity, diabetes mellitus, cirrhosis related to heavy alcohol intake, non-alcoholic fatty liver disease, smoking, and ingestion of aflatoxin.[2,3]

Metastasis of HCC occurs in approximately 30–50% of patients. It primarily metastasizes to lung, bones, and lymph nodes. HCC metastasis to the orbit is a rare phenomenon, more so as a bilateral involvement and first presenting feature. There have been only a few reports of histopathologically proven orbital metastasis from HCC in the past. Almost all cases reported for orbital metastasis secondary to HCC were unilateral cases (Table 1). Herein, we report a case of biopsy-confirmed orbital metastasis of HCC in a 57-year-old man, who first presented with painless bilateral proptosis.

Case report

A 57-year-old man presented with blurred vision in the right eye for 15 days and bilateral, asymmetrical, painless, progressive proptosis of 2 months duration (Fig. 1). It involved the right eye first and then eventually the left eye, but was more severe on the right. He had no known chronic illnesses apart from a history of completed treatment for pulmonary tuberculosis 3 years prior. He denied any alarming social habits, such as smoking and excessive alcohol consumption. The best-corrected visual acuity was 20/60 in the right eye (RE) and 20/20 in the left eye (LE). Examination revealed superior sulcus fullness and bilateral proptosis with Hertel exophthalmometer readings of 24 mm RE and 22 mm LE. There was a mild inferior displacement of the globes. A solid, non-tender, immobile mass was palpable in the right superior sulcus. Ocular motility in both eyes (BE) showed limitations in upgaze. Anterior segment examination revealed conjunctival congestion and chemosis in the RE. There was mild haziness over the right inferior cornea due to exposure keratopathy. LE showed mild congestion

Table 1. Case reports of biopsy-proven orbital metastasis from HCC in the literature to date

	Authors	Age (years)	Sex	Presenting features	Laterality	Remark
1	Lubin (1980)[9]	69	M	Proptosis, pain	R	
2	Zubler (1981)[10]	64	M	Mass at temporal fossa, proptosis, diminished vision, ophthalmoplegia	L	
3	Wakisaka (1990)[11]	58	M	Proptosis, diplopia, ptosis	L	
4	Loo (1994)[12]	71	F	Pain, diminished vision	R	
5	Schwab (1994)[13]	19	M	Proptosis	L	
6	Tranfa (1994)[14]	85	M	Proptosis, pain, diminished vision	R	
7	Kami (1994)[15]	60	M	Proptosis, headache	L	
8	Font (1998)[16]	79	F	Proptosis, pain, diminished vision	R	
9	Scolyer (1999)[17]	77	M	Periorbital mass	R	FNAC
10	Kim (2000)[18]	56	F	Displaced eyeball (orbital mass near lower eyelid)	L	
11	Chen (2003)[19]	69	M	Proptosis, diplopia	R	
12	Gupta (2005)[5]	45	M	Proptosis	L	
13	Oida (2006)[20]	72	M	Diplopia	L	
14	Machado-Netto (2006)[21]	57	M	Proptosis	R	
15	Hirunwiwatkul (2008)[22]	74	F	Proptosis with orbital apex syndrome	R	
16	Pitts (2008)[23] (2 cases)	61	F	Painful proptosis	L	Necropsy
17		47	M	Proptosis, temporal swelling	L	Necropsy
18	Fonseca (2008)[24]	57	M	Painful proptosis	R	
19	Kolarević (2011)[25]	70	M	Painful proptosis	R	

	Authors	Age (years)	Sex	Presenting features	Laterality	Remark
20	Mustapha (2011)[26]	25	M	Painful proptosis	R	FNAC
21	Guerriero (2011)[27]	45	M	Proptosis	L	
22	Jiang (2012)[27]	44	M	Proptosis, diplopia	Both	
23	Piccirillo (2013)[29]	66	M	Mass at medial canthus	L	
24	Eldesouky (2013)[6] (6 cases)	62	M	Painful proptosis	L	
25		70	M	Painful proptosis	L	
26		55	M	Proptosis	R	
27		65	M	Painful proptosis, redness, lacrimation	L	
27		47	M	Painful proptosis	L	
29		62	M	ptosis	R	
30	Chen (2014)[30]	56	M	Epiphora with pulsatile mass in right lacrimal gland	R	
31	Chen (2015)[31]	43	M	Proptosis, headache	L	
32	Kader (2018)[32]	60	M	Swelling at lateral aspect of the eye, blurred vision, pain, watery discharge	L	
33	Present case	57	M	Bilateral proptosis , soft tissue mass	Both	

F: female; FNAC: fine needle aspiration cytology; L: left; M: male; R: right

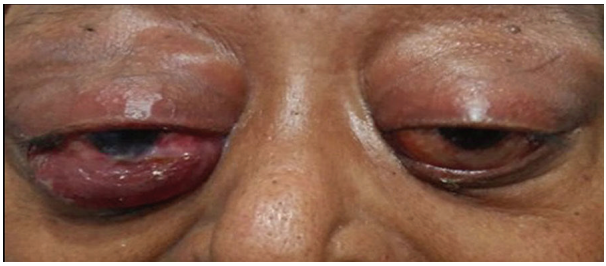

Fig. 1. Bilateral proptosis with exposure keratopathy in RE.

without exposure keratopathy. Pupils were reactive. The intraocular pressure was 18 mmHg in BE. Other anterior and posterior segment examinations were unremarkable in BE.

Orbital computerized tomography (CT) scan showed soft tissue masses in the superotemporal quadrants of both orbits, measuring 3.0 x 3.7 cm in the right and 2.3 x 2.6 cm in the left. There were lytic bone lesions in both lateral walls and right frontal bone (Fig. 2).

We performed percutaneous incisional biopsy from the right orbital mass through a direct sub-brow approach. The lesion was friable and bled severely upon touch. Multiple small pieces were sent for a histopathologic examination. The section revealed fibrous tissue infiltrated by metastatic deposits composed of large polygonal-shaped epithelial cells arranged in a trabeculo-sinusoidal pattern. The cells contained eosinophilic cytoplasm and hyperchromatic nuclei (Fig. 3). The features were consistent with metastatic HCC. We did not perform immunohistochemical studies as there were limited facilities.

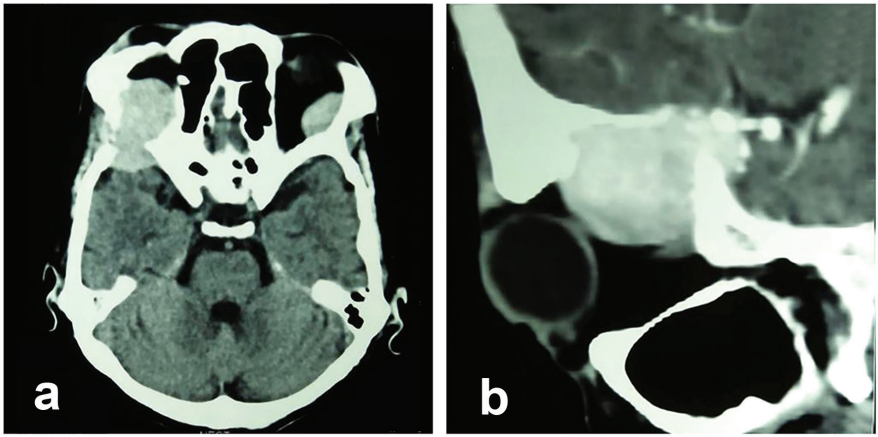

Fig. 2. CT scan. (a) Axial scan showed extraconal soft tissue masses in both orbits. (b) Right frontal bone destruction.

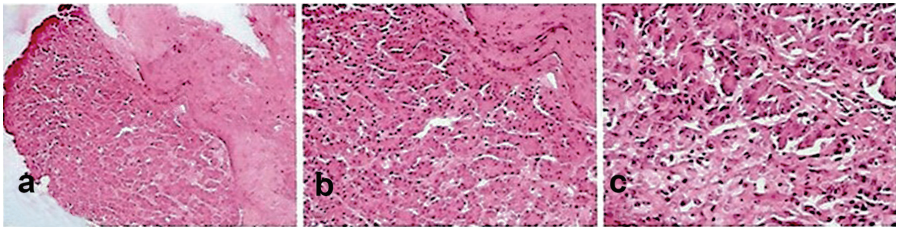

Fig. 3. Histopathological report. (a) 4x: Metastatic tumor deposit. (b) 20x: Tumor cells arranged in trabeculo-sinusoidal pattern. (c) 40x: Features of anaplasia.

We referred the patient for further assessment. Abdominal ultrasound confirmed multifocal HCC with underlying cirrhosis. We planned for further investigations such as hepatitis serology, alfa-fetoprotein, and abdomen CT, but he refused to proceed with investigations and treatment. Informed consent was taken from the patient to share and publish these findings.

Discussion

Orbital metastasis, more so as a bilateral involvement, is a rare phenomenon. When it occurs, ocular manifestations can be the primary presentations without prior history of systemic cancers in 15–19% of cases.[1,4] However, in orbital metastasis, particularly from HCC, it can be as high as 50%.[5,6] Ocular signs from orbital metastasis secondary to HCC often present earlier than that of primary cancer.[7]

Approximately 80–90% of patients with HCC have chronic liver disease and cirrhosis caused by alcoholic liver disease and chronic infection with the hepatitis B and C viruses.[2] In low- and middle-income countries, chronic hepatitis B and C infection is attributed to over 90% of HCC.[3] Our patient did not provide a history of alcohol drinking, and we could not identify the hepatitis serology status as he refused to proceed further. It is pertinent to note that exposure to aflatoxin is a significant risk factor in Southeast Asia, as the humidity in the region favors the contamination of traditional food by the fungus.[2,3]

The histopathological diagnosis of orbital metastasis from HCC is primarily confirmed by the presence of large polygonal cells, trabecular pattern, and endothelial cuffing. Renal cell carcinoma may present with a similar histological feature. The use of carcinoembryonic antigen and alfa-fetoprotein can differentiate HCC from renal cell carcinoma. Immunohistochemical (IHC) markers are useful to diagnose the primary cancers in undifferentiated types of orbital metastasis. In HCC, several markers are available; arginase-1 and hepatocyte paraffin antigen (Hep Par 1) yielded the highest sensitivity for well-differentiated type, whereas combined use of arginase-1 and glypican-3 has 100% sensitivity for poorly differentiated type.[8]

Biopsy-proven orbital metastasis from HCC was first reported in 1980 by Lubin and colleagues.[9] Since then, a few cases have been reported in the literature. We performed a literature search and identified a total of 32 biopsy-confirmed orbital metastasis from HCC to date.[5,6,9-32] It is common in males and aging adults. Most cases presented with proptosis and all cases except one were unilateral. It affects both eyes equally with no significant preference. In one series of 100 patients with orbital metastasis, only 4% had bilateral involvement, and the primary cancers were one each from breast, prostate, cutaneous melanoma, and choroidal melanoma.[1] There was one report of bilateral orbital metastasis involving multiple extraocular muscles from HCC.[28] To our best knowledge, our patient is the first

case presenting with bilateral orbital soft tissue masses from metastatic HCC. Based on imaging findings, many authors reported that HCC metastasizing to the orbits is associated with adjacent bone changes such as bone destruction, bone erosion, and notching.[5,6,22,31] Similarly, our case had lytic changes noted in both lateral walls and right frontal bones adjacent to the tumor masses.

There are multi-disciplinary treatment modalities for orbital metastasis. External beam radiation is the mainstay of treatment. Surgery, adjuvant chemotherapy, immunotherapy, or hormonal therapy can be considered in selected cases. Patients with HCC metastasizing to the orbit have a relatively poor prognosis.[5] Generally, survival is limited to 1.5 years after orbital manifestations irrespective of primary neoplasms.[4]

There are several learning points in this case report. Firstly, it was the first case of biopsy-proven bilateral orbital metastasis involving soft tissue of the orbit. Secondly, HCC may present with bilateral orbital metastasis. Thirdly, this report highlights that orbital metastatic tumors may present as an initial manifestation of undiagnosed systemic cancer and should be considered an important differential diagnosis in cases with bilateral proptosis. Furthermore, we reviewed the previously published data and presented the clinical presentations of orbital hepatocellular metastasis. However, we were unable to analyze the IHC markers for this patient nor the follow-up as the patient refused further management.

Conclusion

Orbital metastatic tumors may present as an initial manifestation of undiagnosed systemic cancer. Although bilateral orbital metastasis is extremely rare, it should be considered when diagnosing patients with bilateral proptosis, and orbital biopsy is crucial for histopathological diagnosis.

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