

Painful Ophthalmoplegia as the Initial Manifestation of Hepatocellular Carcinoma: A Case Report and Literature Review

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Abstract- Primary hepatocellular carcinoma is one of the most common cancers in Taiwan, but orbital metastases are rare. To the best of our knowledge, only 10 cases of metastases to the orbit have been described in the literature. This may be related to the short clinical course of the malignancy and the fact that most patients died before metastasis occurred. We describe a 69-year-old man who developed progressive painful ophthalmoplegia for two weeks. Magnetic resonance imaging of the brain showed a right supra-orbital mass invading the orbital cavity. The diagnosis of hepatocellular carcinoma with orbital metastasis was made after surgical removal of the orbital mass. This is the first reported case of hepatocellular carcinoma with the unusual mode of presentation in Taiwan. We emphasize the importance of early recognition and treatment of this clinical condition.

Key Words: Hepatocellular carcinoma, Metastasis, Orbital, Painful ophthalmoplegia

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INTRODUCTION

Painful ophthalmoplegia often refers to a multiple cranial nerve syndrome involving the oculomotor, trochlear, and abducens nerves and the ophthalmic division of the trigeminal nerve. Various etiologies have been reported; these include infections, inflammations, granulomatous process, sphenoid sinus mucocele, local tumors, dural arteriovenous malformation, trauma, and diabetes mellitus⁽¹⁾. The incidence of orbital metastasis reported in the literature ranges from 2% to 10% of all cases of carcinoma. The incidence seems to be increasing, possibly reflecting progress in treatment of cancer

patients. In 20 to 30% of patients with orbital metastasis, orbital symptoms are the first clinical manifestation of the disease⁽²⁾. Although brain metastasis from hepatocellular carcinoma is relatively common, as is metastasis to the flat bones of the jaw and skull⁽³⁾, orbital metastasis is quite unusual. We describe a case of progressive painful ophthalmoplegia secondary to hepatocellular carcinoma. The literature concerning orbital metastases is also reviewed.

CASE REPORT

A 69-year-old male was hospitalized because of

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double vision especially on upward gaze and progressive drooping of the right eyelid for two weeks. He noted constant dull pain localized in the right half of the forehead which was also exaggerated on upward gaze. On physical examination, a solid, well-defined mass was palpable on the upper margin of the right orbit. There

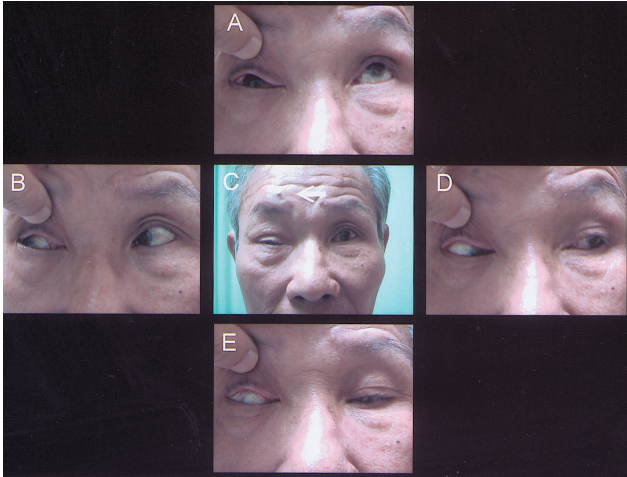


Figure 1. (C) Clinical appearance of the patient with a visible mass (\leftarrow) of the right frontal region. There is ptosis of the right eyelid. (A) Ocular motility of the right eye is decreased on upward gaze. (B) & (D) Ocular motility is normal on horizontal gaze. (E) On downward gaze, motility of the right eye is abnormally increased.

was incomplete ptosis of the right eyelid (palpebral fissure: 3 mm on the right side and 8 mm on the left side), limitations of ocular motility on upward gaze, and inferior displacement of the right eye (Fig. 1). The pupillary light reflex, facial and corneal sensation were not impaired. No proptosis or conjunctival edema was noted.

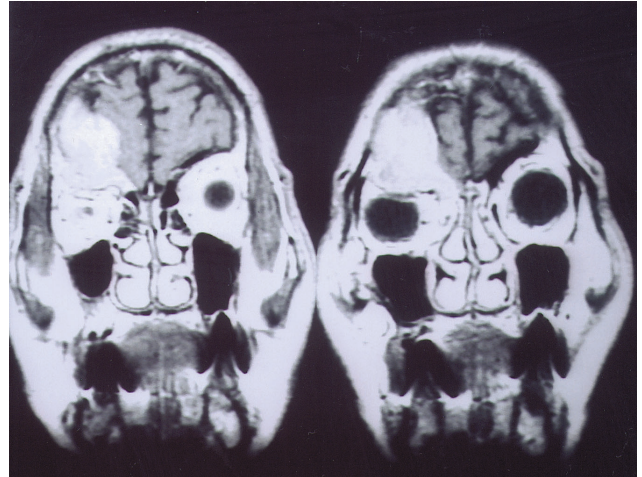


Figure 2. Gadolinium-enhanced magnetic resonance imaging of the brain (coronal view) shows a right supraorbital mass displacing the globe inferiorly, invading the orbital cavity, and extending to the right frontal dural space superiorly.

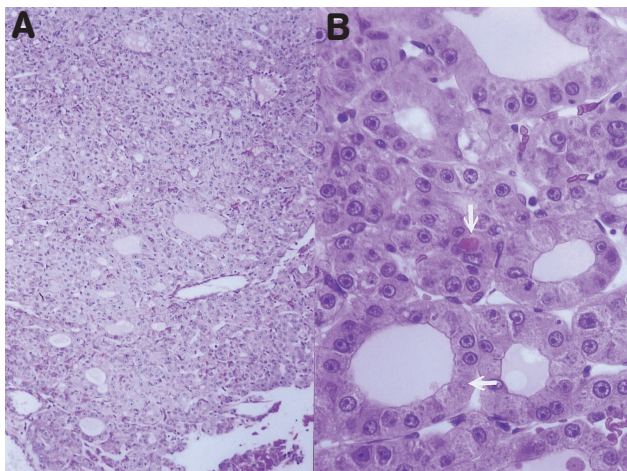


Figure 3. (A) Sections of the orbital mass with oval to polygonal plump hyperchromatic cells arranged in compact trabeculae and with frequent acinar (pseudoglandular) structures (Hematoxylin-eosin stain, original magnification $\times 200$). (B) Bile pigment (\downarrow) found within minute intercellular canaliculi and in some acinar lumens (\leftarrow) (Hematoxylin-eosin stain, original magnification $\times 400$).



Figure 4. Contrast-enhanced computed tomographic scans of the abdomen show a large hypodense mass (9 cm in its greatest diameter) with heterogeneous enhancement in the right lobe of the liver.

Table. Clinical findings in 11 cases of hepatocellular metastasis to the orbit

Source	Age/Sex	Signs & symptoms	Orbital biopsy	Survival
Lubin et al.	69/M	Proptosis	Yes	NS
Zubler et al.	64/M	Proptosis, ophthalmoplegia, decrease vision	Yes	several months
Wakisaka et al.	58/M	Diplopia, ptosis, proptosis	Yes	6 days
Schwab et al.	19/M	Proptosis, exposure keratitis	Yes	2 weeks
Tranfa et al.	85/M	Proptosis, decrease vision, ptosis, pain, chemosis	Yes	NS
Loo et al.	71/F	Decrease vision, pain	Yes	3 months
Kami et al.	60/M	Proptosis, headache	Yes	3.5 months
Phanthumchinda & Hemachuda	29/F	Painful ophthalmoplegia	No (Sternal soft tissue)	NS
Font et al.	79/F	Proptosis, decrease vision, painful ophthalmoplegia, eyeball deviation, chemosis	Yes	Still live after 3 years
Kim et al.	56/F	Eyeball deviation, Ophthalmoplegia	Yes	2 months
Current study	69/M	Painful ophthalmoplegia	Yes	-

*M: male. F: female. NS: not stated.

Laboratory studies, including fasting and postprandial plasma glucose, routine biochemistry tests, erythrocyte sedimentation rate, C-reactive protein, and tumor markers such as α -fetoprotein, were all within normal limits except for a mildly elevated serum transaminase. Magnetic resonance imaging of the brain showed a right supraorbital mass displacing the eyeball inferiorly with invasion into the orbital cavity and extension to the right frontal dural space superiorly (Fig. 2). The right frontal lobe, although compressed, showed no parenchymal reaction. Microscopic surgery through a bifrontal approach was performed with the removal of the tumor. Histopathological findings showed hyperchromatic cells arranged in compact thin trabeculae with acinar formation and bile pigment within minute intercellular canaliculi, indicating hepatocellular carcinoma (Fig. 3). Postoperatively, his ocular symptoms and signs improved markedly. Subsequent abdominal ultrasound and computed tomographic (CT) scans showed a large hypodense mass with heterogeneous enhancement in the right lobe of the liver, compatible with primary hepatocellular carcinoma (Fig. 4). Metastatic bony lesions of the ribs, superior ramus of left pubis, and lumbar vertebrae were noted on bone scan and CT of the pelvis. The patient underwent palliative radiation therapy to the orbit, and the orbital mass regressed significantly.

DISCUSSION

Abdominal pain with a palpable abdominal mass in the right upper quadrant is a common presentation in patients with hepatocellular carcinoma⁽⁴⁾. Occasionally, the tumor manifests with signs and symptoms related to distant metastasis⁽⁵⁾. Orbital metastases from hepatocellular carcinoma are rare, with only ten cases having been reported^(2,3,5-12). Since these metastases often occur in the absence of parenchymal metastases, it is proposed that the route is via Batson's vertebral venous plexus rather than the systemic circulation⁽¹³⁾. The main clinical features in reported cases were proptosis (7/10), ophthalmoplegia (4/10), decreased vision (4/10), orbital pain (4/10), chemosis (3/10), eyeball deviation (2/10) and ptosis (2/10) (Table). Painful unilateral ophthalmoplegia was the initial presentation in our case. Similar findings have been reported previously in two cases^(5,10). In the report of Phanthumchinda et al⁽¹⁰⁾, the lesion was in the superior orbital fissure, and tissue proof was obtained by biopsy of a sternal mass. Initially, the diagnosis was Tolosa-Hunt syndrome and the patient was treated with prednisolone. Clinical improvement was limited. During tapering of the prednisolone, painful ophthalmoplegia recurred and symptoms progressed. In the report of Font et al⁽⁵⁾, the lesion was in the orbit and the patient had marked proptosis, eyelid edema and conjunctival chemo-

sis. She underwent palliative radiation therapy to the orbit with marked improvement. She had lived for three more years after the diagnosis was made. Of all the reported cases, this patient was the only one who survived for more than a year.

Although proptosis was the most common initial manifestation in the previously reported cases (7/10) of metastatic hepatocellular carcinoma to the orbit, this was not true in our case because the tumor extended into the frontal dural space superiorly, and it displaced the eyeball downward. Ptosis and upward gaze paresis in the right eye could be explained by local mechanical damage to the superior division of the third nerve or the muscles it supplies, the superior rectus and the levator palpebrae superioris. The papillary light reflex was intact because the sphincter pupillae and ciliary muscles are supplied by the inferior division of the oculomotor nerve. The abnormalities improved dramatically post-operatively, further supporting the idea that local mechanical damage to the orbital muscles was the most likely mechanism in our patient.

Neurological complications of hepatocellular carcinoma include hepatic encephalopathy due to liver failure in the terminal stage, craniospinal and brain metastases, and paraneoplastic syndrome. Although hepatic encephalopathy is more common than other neurological complications, the awareness of the other possible neurological disorders is important, since palliative treatment in these patients is possible. In summary, metastatic hepatocellular carcinoma should be considered in the differential diagnosis of progressive painful ophthalmoplegia of unknown etiology, especially in Taiwan. Thorough clinical and radiological examination of the patient is required as well as careful histopathological diagnosis of the tumor. Neurologists, ophthalmologists, pathologists and neuroradiologists all play important roles in establishing the correct diagnosis.

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REFERENCES

1. Brazis PW. Localization in Clinical Neurology. 4th ed. Philadelphia: Williams & Wilkins, 2001;8:186
2. Tranfa F, Cennamo G, Rosa N, et al. An unusual orbital lesion: hepatoma metastatic to the orbit. *Ophthalmologica* 1994;208:329-32.
3. Kim IT, Na SC, Jung BY. Hepatocellular carcinoma metastatic to the orbit. *Korean J Ophthalmol* 2000;14:97-102.
4. Isselbacher KJ, Dienstag JL. Carcinomas of the liver. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, eds. *Harrison's Principles of Internal Medicine*. 14th ed. New York: McGraw-Hill, 1998:579-80.
5. Font RL, Maturi RK, Small RG, et al. Hepatocellular carcinoma metastatic to the orbit. *Arch of Ophthalmol* 1998;16:942-5.
6. Zubler MA, Rivera R, Lane M. Hepatoma presenting as a retro-orbital metastasis. *Cancer* 1981;48:1883-5.
7. Wakisaka S, Tashiro M, Nakano S, et al. Intracranial and orbital metastasis of hepatocellular carcinoma: report of two cases. *Neurosurgery* 1990;26:863-6.
8. Schwab L, Doshi H, Shields JA, et al. Hepatocellular carcinoma metastatic to the orbit in an African patient. *Ophthalmic Surg* 1994;25:105-6.
9. Loo KT, Tsui WM, Chung KH, et al. Hepatocellular carcinoma metastasizing to the brain and orbit: report of three cases. *Pathology* 1994;26:119-22.
10. Phanthumchinda K, Hemachuda T. Superior orbital fissure syndrome as a presenting symptom in hepatocellular carcinoma. *J Med Assoc Thai* 1991;74:679-82.
11. Kami H, Wada M, Matsuura T, et al. Case of hepatocellular carcinoma with an orbital metastasis as the initial symptom. *Nippon Naika Gakkai Zasshi - Journal of Japanese Society of Internal Medicine* 1994;83:622-4.
12. Lubin JR, Grove AS Jr, Zakov ZN, et al. Hepatoma metastatic to the orbit. *Am J Ophthalmol* 1980;89:268-73.
13. Posner JB. *Neurological Complications of Systemic Cancer Patients*. Chicago: Year Book Medical Publisher, 1978.