



Acute Painful Ophthalmoplegia in A Patient with Hepatocellular Carcinoma

Wei-Shih Tseng^{1,2}, Yueh-Feng Sung²

¹Department of Diving Medicine, Zuoying Branch of Kaohsiung Armed Forces General Hospital, Kaohsiung, ²Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China

We herein describe a 48-year-old man who developed acute painful ophthalmoplegia of the right eye for 5 days. Magnetic resonance imaging of the brain with contrast detected a contrast-enhancing lesion in the right cavernous sinus (CS) and petrous apex. Tolosa-Hunt syndrome was suspected initially, but later he was diagnosed as CS metastasis from hepatocellular carcinoma (HCC). To the best of our knowledge, only nine similar cases have been reported in the literature. We would like to remind clinicians to consider the possibility of CS metastasis in patients with primary HCC, who present with acute painful ophthalmoplegia.

Key words: Cavernous sinus, hepatocellular carcinoma, ophthalmoplegia, Tolosa-Hunt syndrome

INTRODUCTION

Painful ophthalmoplegia is an uncommon, but important clinical problem to physicians. Clinical approach to patients with painful ophthalmoplegia requires extensive differential diagnoses, including vascular, neoplastic, infectious, and inflammatory lesions.¹ Early diagnosis is essential, and treatment depends on the underlying etiology. In this case report, we describe a patient who developed acute painful ophthalmoplegia of the right eye due to the cavernous sinus (CS) metastasis from hepatocellular carcinoma (HCC).

CASE REPORT

A 48-year-old Taiwanese man with hepatitis B virus (HBV)-related HCC presented to the Emergency Department with a 5-day history of gradual onset of severe boring pain at the medial side of right orbital area and double vision. He denied having head trauma, neck pain, fever, weakness of limbs, or unsteady gait. His past medical history included a right lobectomy of the liver for HCC and transarterial chemoembolization for postoperatively recurrence 10 and 2 years prior to admission, respectively. Sorafenib was prescribed at a starting dose of 200 mg bid because recurrence

of HCC with portal vein thrombosis (cT3bN0M0, stage IIIB) was found again 2 months prior to admission.

His initial vital signs were normal. No conjunctival injection, chemosis, proptosis, facial cellulitis, dental abscess, or neck masses were shown. His pupils were 2.5 mm in size and reactive to light. Visual acuity and fundoscopic examinations were normal in both eyes. Cranial nerve examination revealed a decreased ability to abduct the right eye consistent with abducens nerve palsy. The rest of his cranial nerves and neurological examination was unremarkable. His blood tests revealed increased liver function enzymes (glutamate oxaloacetate transaminase 142 U/L, glutamic pyruvic transaminase 89 U/L, and normal range <41 U/L) and inflammatory markers with a C-reactive protein of 2.5 mg/dL (normal range 0-0.5 mg/dL). His alpha-fetoprotein was >500 ng/ml (normal range 0-20 ng/ml). Infection surveys revealed no obvious infection sources. Chest X-ray showed diffuse and numerous soft-tissue nodules in both lungs, suggesting pulmonary metastases. A computed tomography (CT) of the brain without contrast showed no apparent abnormalities. Magnetic resonance imaging (MRI) of the brain with contrast detected a contrast-enhancing lesion in the right CS and petrous apex [Figure 1]. MR angiography showed no remarkable findings.

After hospitalization, corticosteroid was administered on suspicion of Tolosa-Hunt syndrome (THS). However, there was no improvement of his painful ophthalmoplegia after 72 h of corticosteroid therapy. The patient's orbital pain got progressively worse, and 10 days after admission, he developed right total ophthalmoplegia and ptosis. The diagnosis of HCC with distant metastasis to the CS was made. We recommended the patient receive tissue biopsy to confirm the diagnosis, but he refused. Severe pain in his right eye could only be partially relieved by high dose of narcotic analgesics. He declined

Received: September 25, 2013; Revised: October 28, 2013;
Accepted: December 19, 2013

Corresponding Author: Dr. Yueh-Feng Sung, Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, No. 325, Sec. 2, Cheng-Gong Road, Taipei 114, Taiwan, Republic of China. Tel: +886-2-87923311 ext. 16875; Fax: +886-2-87927174. E-mail: sungyf@mail.ndmctsgh.edu.tw

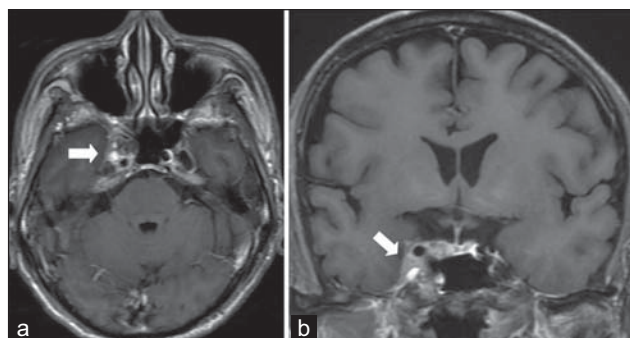


Figure 1. Right cavernous sinus (CS) metastasis from hepatocellular carcinoma. Contrast-enhanced axial (a) and coronal (b) T1-weighted magnetic resonance images showing a lesion involving the right CS (white arrow)

palliative radiotherapy treatment and received hospice care. The patient eventually succumbed to death one and a half months later.

DISCUSSION

Liver cancer is one of the most common causes of malignancies related deaths worldwide, especially in East and South-East Asia.² Among primary liver cancers, HCC represents the major histological subtype, accounting for 70–85% of the total liver cancer worldwide.² Extrahepatic metastases are seen in 37% of patients with HCC.³ Lungs, abdominal lymph nodes, bone marrow, and adrenal glands are commonly metastatic sites of HCC.^{3–5} Brain metastasis from HCC is rare, with a reported frequency ranging from 0.2% to 2.2%.^{4,5}

According to the statistics, breast, lung, and prostate cancers are the most common primary sites with distant metastasis to the CS other than the head and neck cancers.⁶ To date, only nine cases of CS metastasis from HCC were reported in the literature [Table 1].^{7–13} The age of these patients ranged from 40 to 80 years, and 78% of them were male. The majority of them were the carriers of HBV or hepatitis C virus. Most of them died within a short interval ranging from 1 to 12 months after the onset of neurological symptoms, even after surgery or radiotherapy. The management of CS metastasis is palliative.¹⁴ In general, radiotherapy is considered the standard treatment and often results in improvement of symptoms and alleviation of pain.¹⁵ In some patients, early radiosurgery may be associated with improvement of cranial nerve dysfunction.^{15,16} However, the prognosis of HCC with CS metastasis is very poor, and the median survival time is reported to be between 4 and 13 months from the onset of symptoms.^{14,16}

Tolosa-Hunt syndrome is characterized by painful ophthalmoplegia and is caused by an idiopathic granulomatous inflammation of the CS. Corticosteroid is considered to have

Table 1. Summary of case reports on cavernous sinus metastasis from hepatocellular carcinoma

Article	Age/sex	Type of hepatitis	Cranial nerve involvement	Surgical intervention or radiotherapy	Survival time after diagnosis (month)
Morita <i>et al.</i> ^[7]	?	?	?	?	?
Aung <i>et al.</i> ^[8]	40/male	HBV	VI	S	3
Aung <i>et al.</i> ^[8]	71/male	HBV	III, VI	S+RT	12
Kato <i>et al.</i> ^[9]	80/male	HCV	III	RT	2
Kato <i>et al.</i> ^[9]	75/female	HCV	III	RT	?
Kim <i>et al.</i> ^[10]	50/female	HCV	III, IV, VI	—	?
Chen <i>et al.</i> ^[11]	68/male	HBV	?	S+RT	4
Kim <i>et al.</i> ^[12]	51/male	NonHBV/ HCV	III, IV, VI	—	1
Faraji-Rad <i>et al.</i> ^[13]	54/male	?	VI	—	?
Our case	48/male	HBV	III, IV, VI	—	1.5

— = neither surgical intervention nor radiotherapy; ? = unknown;

HBV = hepatitis B virus; HCV = hepatitis C virus; RT = radiotherapy;

S = surgical intervention

diagnostic as well as therapeutic utility. CT scans have been found to be normal in the majority of patients with THS. A contrast-enhanced MRI can play an important role for distinguishing THS from other THS-like entities.¹⁷ MRI of THS shows an enlargement of the CS with isointense to the brain tissue on T1- and T2-weighted images and marked contrast medium enhancement, which is consistent with the MR findings in our patient. Based on the clinical data, our patient was initially diagnosed as THS. However, poor response to steroid therapy prompted us to consider other etiologies. Although the biopsy confirmation was not done in our patient, the progressive neurological deterioration and the evidence of lung metastases were in favor of the diagnosis of HCC with distant metastases to CS.

CONCLUSION

Painful ophthalmoplegia involves various pathological etiologies of CS in a wide spectrum, from inflammation to malignancies. THS should not be considered as the initial diagnosis for a patient who has had a primary malignancy until metastasis has been excluded by appropriate investigation. In addition, if high-dose steroid therapy fails, and neurological findings and pain are progressive, further studies are necessary to exclude other underlying disorders. A high index of suspicion is needed to survey for CS metastasis from HCC when patients with an HCC history present with painful ophthalmoplegia.

DISCLOSURE

All authors declare no competing financial interests.

REFERENCES

1. La Mantia L, Erbetta A, Bussone G. Painful ophthalmoplegia: An unresolved clinical problem. *Neurol Sci* 2005;26 Suppl 2:s79-82.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69-90.
3. Katyal S, Oliver JH 3rd, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastases of hepatocellular carcinoma. *Radiology* 2000;216:698-703.
4. Jiang XB, Ke C, Zhang GH, Zhang XH, Sai K, Chen ZP, *et al.* Brain metastases from hepatocellular carcinoma: Clinical features and prognostic factors. *BMC Cancer* 2012;12:49.
5. Choi HJ, Cho BC, Sohn JH, Shin SJ, Kim SH, Kim JH, *et al.* Brain metastases from hepatocellular carcinoma: Prognostic factors and outcome: Brain metastasis from HCC. *J Neurooncol* 2009;91:307-13.
6. Ahn Y, Yang JH, Kim HJ, Jang SE, Jang YJ, Kim HR, *et al.* Cavernous sinus metastasis of non-small cell lung cancer. *Tuberc Respir Dis* 2010;69:381-4.
7. Morita A, Meyer FB, Laws ER Jr. Symptomatic pituitary metastases. *J Neurosurg* 1998;89:69-73.
8. Aung TH, Po YC, Wong WK. Hepatocellular carcinoma with metastasis to the skull base, pituitary gland, sphenoid sinus, and cavernous sinus. *Hong Kong Med J* 2002;8:48-51.
9. Kato H, Kanematsu M, Goshima S, Kondo H, Nishibori H, Tsuge Y, *et al.* Skull base metastasis from hepatocellular carcinoma revealed by cranial nerve palsy: Reports of two cases. *Eur J Radiol Extra* 2005;54:1-4.
10. Kim SR, Kanda F, Kobessho H, Sugimoto K, Matsuoka T, Kudo M, *et al.* Hepatocellular carcinoma metastasizing to the skull base involving multiple cranial nerves. *World J Gastroenterol* 2006;12:6727-9.
11. Chen SF, Tsai NW, Lui CC, Lu CH, Huang CR, Chuang YC, *et al.* Hepatocellular carcinoma presenting as nervous system involvement. *Eur J Neurol* 2007;14:408-12.
12. Kim SJ, Kim HJ, Lee HW, Choi CH, Kim JU, Do JH, *et al.* Hepatocellular carcinoma with metastasis to the cavernous sinus of skull base causing ptosis. *Korean J Gastroenterol* 2008;52:389-93.
13. Faraji-Rad M, Faraji-Rad E, Mashadinezhad H, Omid A, Rahrooh M. Single cavernous sinus metastasis as the first manifestation of hepatocellular carcinoma - A rare case report and review of literature. *Neurosurg Q* 2010;20:203-7.
14. Spell DW, Gervais DS Jr, Ellis JK, Vial RH. Cavernous sinus syndrome due to metastatic renal cell carcinoma. *South Med J* 1998;91:576-9.
15. Laigle-Donadey F, Taillibert S, Martin-Duverneuil N, Hildebrand J, Delattre JY. Skull-base metastases. *J Neurooncol* 2005;75:63-9.
16. Kano H, Niranjana A, Kondziolka D, Flickinger JC, Lunsford LD. The role of palliative radiosurgery when cancer invades the cavernous sinus. *Int J Radiat Oncol Biol Phys* 2009;73:709-15.
17. Cakirer S. MRI findings in the patients with the presumptive clinical diagnosis of Tolosa-Hunt syndrome. *Eur Radiol* 2003;13:17-28.