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Letter to the Editor: New Observation

Hepatocellular Carcinoma Metastasis Presenting as Isolated Third Nerve Palsy

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Hepatocellular carcinoma (HCC) is an aggressive form of hepatic cancer that is typically diagnosed in patients with underlying liver dysfunction. Life expectancy following diagnosis of HCC is dependent on the staging and extent of disease, but prognosis is generally poor with a median survival ranging from 11 to 15 months.[1] Ocular symptoms caused by HCC metastasis are uncommon, and most often occur due to orbital metastasis with proptosis being the most frequent finding.[2] Very rarely, skull base metastasis can cause ocular symptoms, although typically late in the disease course or in the setting of other extensive liver damage.[3–7] Visual symptoms as the presenting manifestation of HCC are extremely rare.[2] To the best of our knowledge, this is the first report of metastatic HCC manifesting as an isolated cranial nerve palsy, without any previously known liver disease. We describe an otherwise asymptomatic patient presenting with a third nerve palsy, who was subsequently found to have metastatic HCC to the skull base.

A 72-year-old man was referred for a 3-month history of binocular horizontal diplopia. He denied any associated neurologic or systemic symptoms. On examination, he had mild ptosis and was exotropic with limitation of supraduction, infraduction, and adduction in the left eye, consistent with a pupil-sparing left third cranial nerve palsy. The remainder of the ocular examination was normal. His comorbidities were significant for diabetes, hypertension, hypercholesterolemia, and a heart attack that required a cardiac stent.

Urgent head computed tomography (CT) was completed which demonstrated a 3.3 cm enhancing lytic lesion in the central skull base, superior to the clivus. The lesion extended into the left cavernous sinus with presumed involvement of the third cranial nerve (Figure 1). Subsequent magnetic resonance imaging confirmed a large mass in the clivus consistent with bone metastasis (Figure 2).

CT thorax located the primary mass on the left lobe of the liver measuring greater than 9 cm with no pulmonary metastasis. Tumor markers showed a CA-19-9 of 13 U/mL (normal: ≤34 U/mL) and an alpha-fetal protein of 13.3 μg/L (normal: ≤7.0 μg/L). Although this patient had no history of liver disease, his platelet count was borderline low at 150×10^9/L (normal: $150–400 \times 10^9$/L) and dropped to 130×10^9/L the following month, with elevated alkaline phosphatase (188 U/L, normal: 40–129 U/L) and aspartate aminotransferase (66 U/L, normal: ≤40 U/L). All additional blood work was normal. A biopsy of the skull base mass revealed tumor cells positive for pan-cytokeratin (A1–4) and arginase (A1–7), and negative for cytokeratins 7 (A1–5) and 20 (A1–6). The immunohistochemical profile and morphology was in keeping with metastatic hepatocellular carcinoma. The skull base metastasis was treated with external beam radiotherapy followed by transarterial chemoembolization and yttrium-90 (Y90) radioembolization of the primary tumor. At 20 months post-diagnosis, the patient was undergoing treatment with chemotherapy with stable metastatic disease on imaging.

We present a case of HCC metastatic to the skull base resulting in a third cranial nerve palsy. Ocular manifestations of metastatic HCC have rarely been reported and typically involve orbital metastasis.[2] Only a small number of cases have reported ocular symptoms caused by skull base metastases, all of them occurring in the setting of long-standing HCC, hepatitis infection, excessive alcohol consumption, or other history of extensive liver damage.[3–7] To our knowledge, no prior cases of metastatic HCC have presented with an isolated third cranial nerve palsy. Although rare, this case highlights how compressive lesions can cause a third cranial nerve palsy without pupillary involvement, reinforcing the need for urgent imaging of all third cranial nerve palsies.

Diagnosis of HCC typically occurs in the context of preexisting liver damage and most metastases occur in patients with known HCC.[1] Hepatitis B, hepatitis C, alcoholic liver cirrhosis, and nonalcoholic steatohepatitis are the most recognized risk factors contributing to HCC.[1] Our patient's low platelet count alongside his elevated alkaline phosphatase and aspartate aminotransferase may have been suggestive of some hepatic dysfunction; however, he had not been previously diagnosed with liver disease, did not consume excessive alcohol, and had no related symptoms. Previously documented cases of ocular symptoms caused by HCC metastasis to the skull are associated with extensive liver damage, which may contribute to the very poor reported prognosis.[7] Conversely, our patient was still alive and undergoing treatment 20 months after his diagnosis and he did not have any previously documented liver damage.

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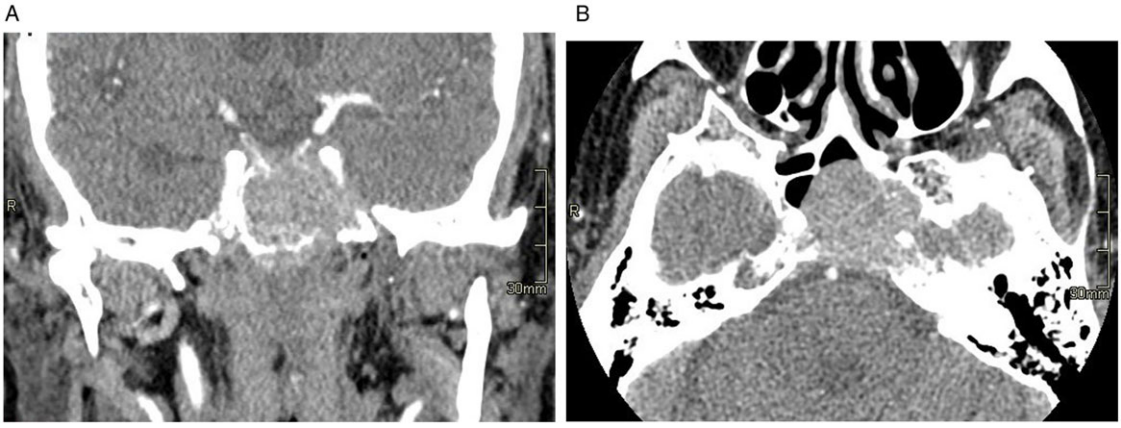


Figure 1: CT head coronal (A) and axial (B) slices with contrast revealing a large, mildly enhancing lesion in the central skull base involving the clivus, with extension into the sphenoid sinuses bilaterally and the left cavernous sinus. The mass has eroded the sellar floor and is in contact with the basilar artery and encasing the left petrous carotid artery.

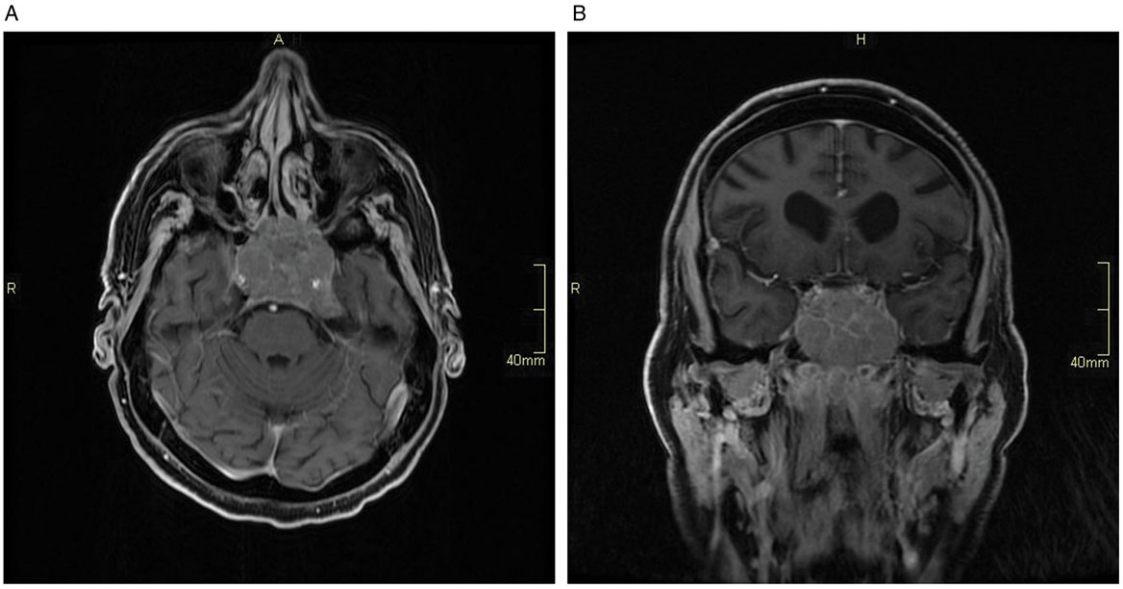


Figure 2: Axial (A) and coronal (B) T1 post-contrast MRI head sequences demonstrating a large expansile mass (45 mm × 31 mm× 38 mm) centered in the clivus and contacting the medial margins of the petrous carotid arteries.

Orbital metastasis is the most frequent cause of ocular symptoms associated with HCC,[2] with only a small number of cases reporting ocular symptoms due to skull base metastasis.[3–7] Proptosis, with or without pain, is the most common ocular symptom associated with HCC although diplopia, decreased vision, ophthalmoplegia, and ptosis have also been reported.[2] Metastasis is typically associated with advanced stages of previously diagnosed HCC or other extensive liver damage, but may rarely be the presenting symptom that leads to a diagnosis of HCC.[3–5,7] Earlier detection of HCC through the recognition of ocular symptoms may prompt earlier treatment and prolong survival.

Due to improved treatment options and increased survival, the rates of extrahepatic HCC manifestations are anticipated to increase.[8] Extrahepatic manifestations typically occur with advanced stage primary tumors that are either larger than 5 cm, as in our patient, or involve large vessel vascular invasion.[8] As treatment for HCC advances and patients live longer, understanding the extrahepatic manifestations of HCC becomes more relevant.

In summary, we describe a unique case of a 72-year-old man with a third cranial nerve palsy as the presenting manifestation of HCC metastasis to the skull base, without any previously documented liver damage or other systemic symptoms. This case underscores the importance of imaging all third nerve palsies, even in the absence of pupil involvement, and the crucial role ophthalmologists can play in diagnosing systemic disease.

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Statement of Authorship. NP: literature review, manuscript writing (original draft), AB: image production, manuscript writing (review and editing), LB: conceptualization, manuscript writing (review and editing), supervision.

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