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CASE REPORT

Distant metastasis of hepatocellular carcinoma to Meckel's cave and cranial nerves: A case report and review of literature

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Abstract

BACKGROUND

Metastasis occurs as a late event in the natural history of hepatocellular carcinoma (HCC), and most patients die of liver failure attributed to the tumor supplanting the liver. Conversely, the brain is a less common metastatic site.

CASE SUMMARY

We describe a rare case of hepatitis C virus-related multiple HCC metastasizing to the cavernous sinus, Meckel's cave, and the petrous bone involving multiple cranial nerves in an 82-year-old woman. At admission imaging studies including Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (MRI) revealed multiple HCC nodules in both right and left lobes. Ultrasound guided biopsy of the left lobe revealed moderately differentiated HCC. Molecular targeted therapy with Lenvatinib (8 mg/d for 94 d, *per os*) and Ramucirumab (340 mg/d and 320 mg/d, two times by intravenous injection) were administered for 4 mo, resulting in progression of the disease. Three months after the start of molecular target therapy, the patient presented with symptoms of hyperalgesia of the right face and limited abduction of the right

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eye, indicating disturbances in the right trigeminal and abducens nerves. Brain MRI disclosed a mass involving the cavernous sinus, Meckel's cave and the petrous bone. Contrast-enhanced MRI with gadolinium-chelated contrast medium revealed a well-defined mass with abnormal enhancement around the right cavernous sinus and the right Meckel's cave.

CONCLUSION
The diagnosis of metastatic HCC to the cavernous sinus, Meckel's cave, and the petrous bone was made based on neurological findings and imaging studies including MRI, but not on histological examinations. Further studies may provide insights into various methods for diagnosing HCC metastasizing to the craniospinal area.

Key Words: Meckel's cave; Abducens nerve; Trigeminal nerve; Hepatocellular carcinoma; Magnetic resonance imaging; Case report

Core Tip: We describe a case of hyperalgesia of the right side of the face and limited abduction of the right eye caused by hepatocellular carcinoma (HCC) metastasizing to the right cavernous sinus, the right Meckel's cave, and the right petrous bone diagnosed through neurological findings and imaging studies. Although HCC metastasizing to the cavernous sinus, Meckel's cave and the petrous bone is rare, clinicians need to be vigilant when the patients show neurological dysfunction, especially cranial nerve involvement.

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INTRODUCTION

Hepatocellular carcinoma (HCC), the most common liver cancer, is considered to bring more than 25 hundred thousand deaths worldwide every year. Metastasis is one of the most major points influencing prognosis. HCC often involves metastasis in the liver, but metastasis out of the liver to the lung, bone, and adrenal glands is less frequent, whereas the brain is commonly not connected. The authors report a case of hyperalgesia of the right side of the face and limited abduction of the right eye caused by HCC metastasizing to the right cavernous sinus, the right Meckel's cave, and the right petrous bone diagnosed through neurological findings and radiological studies.

CASE PRESENTATION

Chief complaints

An 82-year-old woman was in November 2019 admitted to Kobe Asahi Hospital for the treatment of HCC with molecular targeted therapy such as Lenvatinib (LEN) (8 mg/d).

History of present illness

She had overcome hepatitis C virus infection (HCV) 10 years earlier with interferon treatment, but still retained Child A liver cirrhosis.

History of past illness
She has suffered from chronic obstructive pulmonary disease for 20 years.

Personal and family history
Nothing particular.

Physical examination
She had no hepatomegaly and no splenomegaly.

Laboratory examinations
Laboratory examinations at admission revealed the following: Total protein 7.3 g/dL (normal 6.5-8.3), albumin 3.6 g/dL (3.8-5.3), aspartate aminotransferase 92 IU/L (10-40), alanine aminotransferase 172 IU/L (5-40), gamma-glutamyl transpeptidase 90 IU/L (< 35), alkaline phosphatase 422 IU/L (115-359), T-bil 1.3 mg/dL (0.2-1.2), NH3 163 μg/dL (< 130), pertussis toxin 88.3% (70-130), white blood cell 67 × 10^3/μL (36-90), Hb 13.6 g/dL (11.5-15.0), platelets 32.0 × 10^4/μL (13.4-34.9), hepatitis B surface antigen (-), HCVAb (+), HCV RNA (-), tumor markers were as follows: Alpha-fetoprotein (AFP) 30332.7 ng/mL (< 10.0), PIVKA-II 1395 mAU/mL (< 40) (Table 1).

Imaging examinations
Imaging examination 1: At admission imaging studies including Gadolinium-ethoxy-benzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (MRI) showed multiple HCC nodules in both right and left lobes (Figure 1A). Gastrointestinal fiberscope revealed atrophic gastritis.

Imaging examination 2: Brain MRI revealed high intensity in the bilateral globus pallidus on T2-weighted images (T2WI), ascribed to elevated serum ammonia (163 μg/dL), but no findings in the cavernous sinus or Meckel's cave (Figure 1B), and marrow in the petrous bone was intact (Figure 1C).

Imaging examination 3: Brain MRI revealed a low intensity mass around the right Meckel's cave on T2WI (Figure 1D) and loss of normal fatty bone marrow signal intensity in the right petrous bone on T1-weighted images (T1WI) (Figure 1E).

Imaging examination 4: MRI revealed a low intensity mass around the right cavernous node, the right Meckel's cave, and the right petrous bone on T2WI (Figure 1F). Based on MRI findings, the rapid increase in the size of the lesions over 1 mo and the onset of neurologic dysfunction, such as impairment of right trigeminal and abducens nerves, were most likely due to the metastasizing HCC.

Histopathological examinations
Ultrasound guided biopsy of the left lobe revealed moderately differentiated HCC (Figure 1G).

FINAL DIAGNOSIS
Contrast-enhanced MRI with gadolinium-chelated contrast medium revealed a well-defined mass with abnormal enhancement around the right cavernous sinus and the right Meckel's cave (Figure 1H).

TREATMENT
Molecular targeted therapy with LEN (8 mg/d for 94 d, *per os*) and Ramucirumab (340 mg/d and 320 mg/d, two times by intravenous injection) were administered for 4 mo, resulting in progression of the disease. Two months after the start of molecular targeted therapy, tumor markers were as follows: AFP 3830 ng/mL, PIVKA-II 3782 mAU/mL.

Three months after the start of molecular targeted therapy, tumor markers were as follows: AFP 25761 ng/mL, PIVKA-II 13045 mAU/mL. The patient demonstrated hyperalgesia of the right side of the face and limited abduction of the right eye.

Four months after the start of molecular targeted therapy, tumor markers were as follows: AFP 226112 ng/mL, PIVKA-II 268638 mAU/mL, carcinoma embryonic

Table 1 Laboratory data on admission

Parameters	Results	Parameters	Results
WBC	67 × 10^3/μL	ALP	422 IU/L
Hb	13.6 g/dL	γ-GTP	90 IU/L
Platelets	32.0 × 10^4/μL	NH3	163 μg/dL
PT	88.3%	HBsAg	(-)
TP	7.3 g/dL	HCVAb	(+)
ALB	3.6 g/dL	HCV RNA	(-)
T-bil	1.3 mg/dL	AFP	30332.7 ng/mL
AST	92 IU/L	PIVKA-II	1395 mAU/mL
ALT	172 IU/L		

WBC: White blood cell; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALB: Albumin; TP: Total protein; PT: Pertussis toxin; AFP: Alpha-fetoprotein; HCV: Hepatitis C virus; HBsAg: Hepatitis B surface antigen; ALP: Alkaline phosphatase; γ-GTP: Gamma-glutamyl transpeptidase.

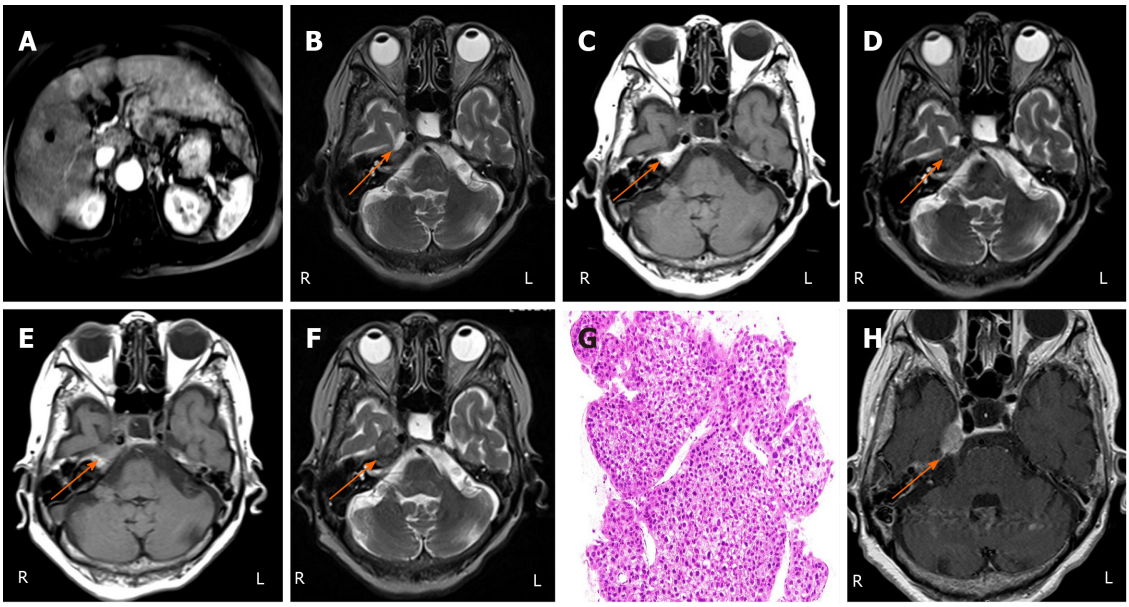

Figure 1 Imaging findings and histopathological findings. A: Ethoxybenzyl magnetic resonance imaging (MRI), hypervascular hepatocellular carcinoma (HCC) in the right and left lobes; B: Brain MRI [T2-weighted image (T2WI)], no findings in the cavernous sinus or Meckel's cave; C: Brain MRI [T1-weighted image (T1WI)], intact findings of bone marrow in the petrous bone; D: Brain MRI (T2WI), low intensity mass in the right Meckel's cave (arrow); E: Brain MRI (T1WI), loss of normal fatty bone marrow signal intensity in the right petrous bone (or apex); F: Brain MRI (T2WI), low intensity mass around the right cavernous node, the right Meckel's cave, and the right petrous bone on T2WI; G: Histopathological finding (hematoxylin and eosin staining), moderately differentiated HCC; H: Contrast enhanced MRI, well-defined mass with abnormal enhancement in the right cavernous sinus, and the right Meckel's cave (arrow). L: left; R: Right.

antigen 3.7 ng/mL (< 5.0), CA19-9 126.8 U/mL (< 37.0), interleukin-2R 824 U/mL (122-496).

Five months after the start of molecular targeted therapy, tumor markers were as follows: AFP 26795 mg/dL, PIVKA-II 258061 mAU/mL.

OUTCOME AND FOLLOW-UP

Based on the diagnosis, γ knife treatment was performed resulting in relief of the right side of the hyperalgesia. Fourteen days after γ knife treatment, the patient died due to the worsening of general condition.

DISCUSSION

Metastasis occurs as an advanced incident in the clinical course of liver cancer, and most patients expire because of hepatic insufficiency due to the cancer supplanting the liver. Distant metastases are routinely discovered at autopsy in over 50% of the cases [1-3]. On the contrary, the brain is an uncommon metastatic location. Accidental distant lesions at such more unusual locations are less a considered as possible metastases when metastatic HCC is not discovered at the more usual locations (the lungs, lymph nodes, and bone)[1-3].

The central nervous system is an uncommon location of metastatic HCC[4-8]. Before 1990, the diagnosis of HCC metastasizing to the craniospinal place was evidenced by histopathological findings of biopsy, operative and post-mortem tissues. Lately diagnosis is confirmed by neurologic tests and radiological findings, including computed tomography (CT) and MRI due to advances in such examinations[9-13]. In the 20th century, seven cases of HCC presenting as brain metastasis with no overt liver connection have been reported: Distant metastasis of liver cancer to the cerebrum in one case, and to the cranium in 6 cases[8]. Each showing slightly unusual hepatic examination early assessed, led to the diagnosis that in brain metastasis of obscure origin in a place where it is a usual illness, liver cancer should be viewed in differential diagnoses[8]. In Japan as in Taiwan, the place where liver cancer is a usual illness, HCC metastasizing to the cranium base relating to plural cranial nerves has not been described until now, but one case of cranium metastasis related to emergent epidural HCC[9].

After the 20th century, several cases of metastatic HCC to the cranial nerves have been reported: A 50-year-old female with HCV-associated recurrent multiple HCC metastasizing to the skull base involving multiple cranial nerves shows with conditions drop of eyelid, settlement of the right eyeball, and left abducens paralysis, suggesting disabilities of the right oculomotor and trochlear nerves, and both side abducens nerves. Contrast-enhanced CT of the brain shows an indistinct tumor with unusual increase surrounding the sella turcica. Brain MRI reveals that the tumor involves the clivus, the cavernous sinus, and the petrous apex. On contrast-enhanced MRI with gadolinium-chelated contrast medium, the tumor shows imbalanced middle increase. The diagnosis of metastatic liver cancer to the skull base is done based on of neurologic studies and radiological findings such as CT and MRI, but not on histopathological findings[13].

Two patients with HCC metastasizing to the skull base, the pituitary gland, the sphenoid sinus, and the cavernous sinus present with diplopia, retro-orbital headache, and multiple cranial nerve palsies. One is diagnosed with HCC prior to transsphenoidal operation of the pituitary metastasis. The second patient is, with histopathological examination, diagnosed to have HCC signs and symptoms associating with the primary tumor[14].

Two cases of HCC metastasizing to the cavernous cavity and the sphenoid cavity presenting with double vision and back eye socket headache, are performed operation for primary pituitary gland tumors. After operation, both cases are diagnosed as metastases from HCC[15].

A 73-year-old woman with HCV-related HCC shows a slightly limited abduction, more focused on the left eye with horizontal double vision. MRI of the face and paranasal cavity reveals a tumor in the left sphenoid cavity (22 mm × 16 mm × 16 mm) that invades the cavernous cavity and the forward slope of Meckel's cave[16,17]. HCC cases of metastasis to the brain from literature were summarized in Table 2 [Age: 56 (25-82), male: 16, female: 7]. Meckel's cave, a natural mouth-shaped aperture measuring 4 mm × 9mm wide at its opening and 15 mm in length within petrous apex's meningeal dura propria and periosteal layers, is the central part of the mid cranial fossa; it plays as a main route for the biggest cranial nerve (the fifth)[18,19]. The cavernous sinus is an important element of the cranial vascular organization, having immediate or indirect relations with the cerebrum, cerebellum, brainstem, face, eye, eye socket, nasopharynx, mastoid, and middle ear[20,21].

The neural components inside the cavernous sinus contain the sympathetic carotid plexus and 4 cranial nerves. The sites of these nerves, in superior to inferior turn, are the oculomotor (the third), trochlear (the fourth), abducens (the sixth), and ophthalmic divisions of the trigeminal (the fifth)[20].

Differential diagnosis of Meckel's cave lesions includes neoplastic and non-neoplastic ones.

Meckel's cave tumors account for only 0.5% of all intracranial tumors. Neoplastic lesions are trigeminal schwannoma (the most common with -33% of cases)[22], meningioma[22,23], pituitary macroadenoma, metastases: Including retrograde spread

Table 2 Hepatocellular carcinoma cases of metastasis to the brain from literature

No	Age	Sex	Presenting symptoms	Site of metastasis	Survival (from the onset of symptoms)	Ref.
1	25	M	Headache and left weakness	Right temporoparietal brain	1 d	Chang and Chen[5], 1979
2	50	M	Weakness of right leg, focal seizure of right leg	Calvarium of the skull, dura, brain	3 mo	Chang and Chen[5], 1979
3	51	F	Epistaxis, ptosis, diplopia, facial weakness in the left side	Skull base	6 mo	Chang and Chen[5], 1979
4	64	M	Loss of vision in the left eye, anorexia, weight loss	Lateral aspect of the temporal fossa and in the anterior portion of the middle cranial cavity	3 mo	Zubler *et al* [7], 1981
5	59	M	Left arm weakness and numbness, headache with left weakness, disturbed consciousness	Brain parenchyma (right frontotemporal parietal) with intracranial haemorrhage	2 mo	Lee[8], 1992
6	58	F	Progressive enlarging scalp mass over vertex for 4 mo	Calvarium, dura, brain parenchyma	10 mo	Lee[8], 1992
7	48	F	Progressive enlarging scalp mass over the left parietal and right frontal region for 6 mo	Calvarium	8 mo	Lee[8], 1992
8	36	M	Progressive enlarging scalp mass in right occipital region for 2 mo	Calvarium	3 mo	Lee[8], 1992
9	60	M	Diplopia and proptosis for 2 mo. Ophthalmoplegia for 1 mo	Skull base (retrobulbar)	7 mo	Lee[8], 1992
10	54	M	Progressive dysarthria and atrophy of left tongue for 2 mo	Skull base (jugular fossa hypoglossal canal)	4 mo	Lee[8], 1992
11	47	M	Right hemicrania for 3 mo blurred vision with ptosis and limitation of eye movement (OD) numbness on the right forehead for one month	Skull base (parasellar)	6 mo	Lee[8], 1992
12	70	M	Left-sided weakness	Acute epidural hematoma adjacent to the right parietal bone	2 mo	Hayashi *et al* [9], 2000
13	58	F	Progressive weakness of her right leg, right hemianesthesia and weakness	Left parietal region, left high parietal area	6 mo	Lee and Lee [11], 1988
14	50	M	Hemiparesis and numbness of left upper arm, explosive headache and vomiting, disturbance of consciousness	Right frontotemporoparietal area	2 mo	Lee and Lee [11], 1988
15	65	M	Progressive painful right sided proptosis and ptosis, intermittent right temporal and facial pain, loss of sensation on the right side of the face	Right orbital apex	9 d	Phadke and Hughes[12], 1981
16	55	M	Mild right weakness	Left fronto-parietal cerebral hemisphere	11 d	Phadke and Hughes[12], 1981
17	50	F	Ptosis, diplopia, left abducens palsy	Clivus, cavernous sinus, petrous apex	Not described	Kim *et al*[13], 2006
18	40	M	Diplopia, retro-orbital headache, and occasional vomiting	Pituitary fossa, clivus, sphenoid sinus, and right petrous apex	3 mo	Aung *et al* [14], 2002
19	71	M	Headache, diplopia, ptosis of the right eye	Pituitary gland, optic chiasma, cavernous sinus	1 yr	Aung *et al* [14], 2002
20	67	M	Diplopia, left retro-orbital headache	Sphenoid sinus, pituitary gland, clivus	15 mo	Tamura *et al* [15], 2013
21	58	M	Headache, visual disturbance, general fatigue, diplopia, oculomotor nerve palsy	Pituitary fossa, cavernous sinus	3 wk	Tamura *et al* [15], 2013
22	73	F	Frontotemporal and left periorbital headache with associated photophobia	Left sphenoid sinus, cavernous sinus	Not described	Morais *et al* [16], 2018
23	82	F	Hyperalgesia of the right face and limited abduction of the right eye	Cavernous sinus, Meckel's cave, petrous bone	5.5 mo	Our case

of head and neck tumors[24-27], epidermoid cysts[28], lipoma, base of skull tumors. All these tumors should be differentiated from Meckel's cave tumors.

Non-neoplastic lesions include internal carotid artery aneurysms/vascular malformation[29,30], and petrous apex cephalocele.

In our case, benign neoplasms such as schwannoma, meningioma, pituitary macroadenoma, epidermoid cyst, lipoma, base of skull tumors, as well as internal carotid artery aneurysms, vascular malformation and petrous apex cephalocele were ruled out in differential diagnosis.

In our case, brain MRI (T1WI and T2WI) disclosed a mass involving the right cavernous sinus, the right Meckel's cave and the right petrous bone; MRI with contrast medium revealed abnormal enhancement around the right cavernous sinus, and the right Meckel's cave.

Moreover, no other malignancies, or lymphoma, have been observed clinically; metastasis from HCC is most likely, irrespective of the absence of histological findings.

CONCLUSION

Taken together with neurological and imaging findings, our case was diagnosed as metastatic HCC to the right cavernous sinus, the right Meckel's cave and the right petrous bone involving multiple cranial nerves including the right fifth, and sixth.

The diagnosis of HCC metastasizing to this area is difficult to confirm by histopathological examination because of the deep-seated location and the neurovascular structures; nevertheless, histopathological diagnosis of HCC metastases to the pituitary gland bone has been reported[13,14].

In a previous study, the reason for HCC metastasis to the skull base was explained by the long survival of 15 years with various treatment regimens of chemotherapy and chemoembolization[13]. In our case, HCC metastasis may be due to the biological behavior of HCC such as being moderately differentiated and the failure of molecular targeted therapy, resulting in disease progression.

To our knowledge, our case is the second case of HCC metastasizing to the cavernous sinus, and Meckel's cave.

Although HCC metastasizing to the cavernous sinus, Meckel's cave and the petrous bone complicating multiple cranial nerves is very exceptional, medical professionals should be careful and good at managing radiological examinations including CT and MRI, when the patients show neurologic dysfunction, especially cranial nerve connection.

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