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Skull Metastasis From Intrahepatic Cholangiocarcinoma: Report of 3 Cases and Review of the Literature

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Abstract

Skull metastases occur in patients with various malignancies; however, those resulting from intrahepatic cholangiocarcinoma (ICC) have been rarely reported. In our hospital, 324 patients were diagnosed with metastatic brain or skull tumors from June 1969 to June 2011, but only 3 of them (0.9%) developed skull metastases from ICC. We report the case of 3 patients with skull metastases from ICC. A combination of computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), and methionine-PET were used for imaging. Sites of tumors were the lateral left orbit and right parietal bone in case 1, the left parietal bone, left temporal bone, and lateral left orbit in case 2, the right petrous bone, right occipital bone, and upper cervical vertebra in case 3. The metastases were confirmed to have originated from ICC by biopsy in two of the cases and diagnosed by MRI and FDG-PET in case 2. Radiosurgery and radiotherapy had positive effects on symptom improvement and cosmetic problems.

Key words: intrahepatic cholangiocarcinoma, metastasis, skull, Batson's plexus

Introduction

Blood-borne metastases from various malignancies develop occasionally in the skull. Common primary sites include breast, lung, and prostate cancers and malignant lymphomas.[9] Skull metastases are often asymptomatic and clinically less important than intraparenchymal metastases. However, in symptomatic cases with local pain or cranial nerve palsies, treatment is necessary to improve the patients' quality of life.[7–9,14]

Intrahepatic cholangiocarcinoma (ICC) is a malignant tumor that originates from cholangiocytes of small intrahepatic bile ducts. It is relatively rare, accounting for 5–10% cholangiocarcinomas, which account for only 3% of all gastrointestinal cancers.[6,11]

Malignant ICC cells tend to spread lymphogenously; therefore, frequent metastatic locations include the liver, intra-abdominal lymph nodes, peritoneum, and lungs. Brain or skull metastasis is very rare.[12] In our hospital, 324 patients were diagnosed with brain or skull metastases from June 1969 to June 2011, but only 3 of them (0.9%) developed skull metastases from ICC; no patient had brain metastases from ICC. We report these 3 cases.

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Case reports

Case 1: A 56-year-old female had undergone hepatotomy for ICC. Her follow-up included repeat computed tomography (CT) and showed no recurrence.

In the same year of hepatotomy, she complained of pain and swelling around her left eyelid, which disappeared within 4–5 days but recurred several times. She was initially treated by an ophthalmologist, but the symptom did not improve. Two years later, she came to our hospital following magnetic resonance imaging (MRI) that revealed a left intraorbital tumor. Physical examination revealed left eyelid swelling. Ophthalmic examination showed no abnormality. Serum carcinoembryonic antigen (CEA) and carbohydrate antigen(CA)19-9 levels were within normal ranges. CT showed uniformly enhanced masses in the lateral left orbit and right parietal bone; both accompanied bone destruction (Fig. 1a, b). Gd-DTPA-enhanced MRI (Gd-DTPA: gadolinium diethylenetriaminopentaacetic acid) showed slight hypointensity and isointensity on T_1- and T_2-weighted images, respectively, for both lesions (Fig.

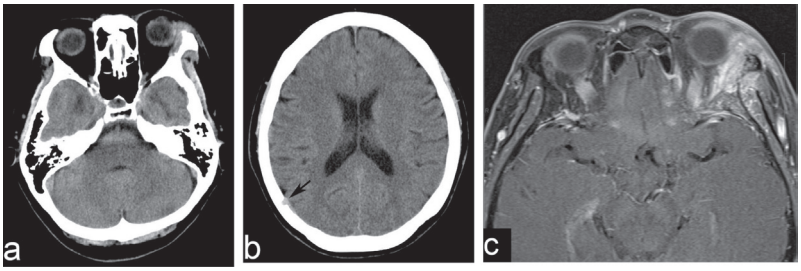

Fig. 1 Postcontrast CT showing uniformly enhanced masses in the lateral left orbit (a) and right parietal bone (b); both were accompanied by bone destruction. Contrast-enhanced T_1-weighted MRI of the lesions (c). The lateral lesion of the left orbit partially invaded bone, muscle, and the dura mater. CT: computed tomography, MRI: magnetic resonance imaging.

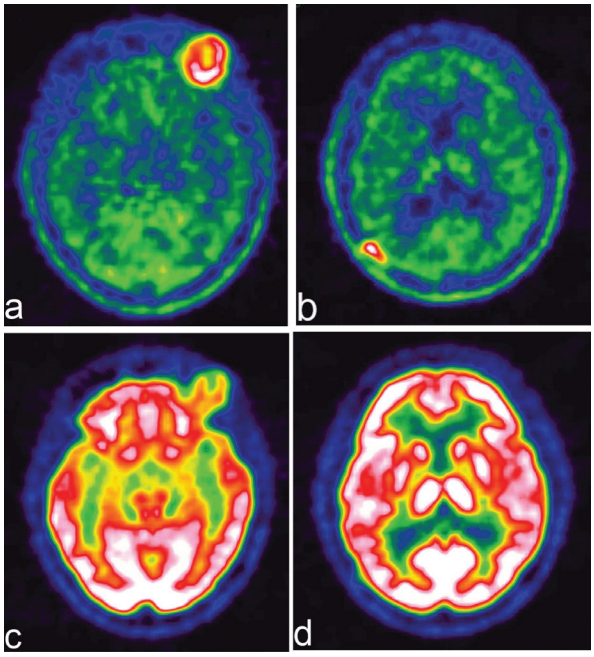

Fig. 2 Methionine-PET showing high uptake by the lateral left orbit (a) and right parietal bone (b). FDG-PET (c, d) also shows high uptake by the same lesions, which was less obvious than that shown by methionine-PET. FDG-PET: 18F-fluorodeoxyglucose positron emission tomography.

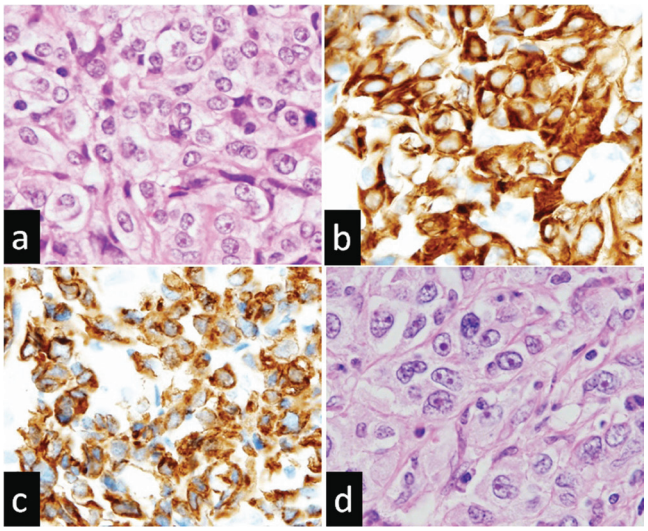

Fig. 3 Histopathological examination of the lateral lesion of the left orbit (a, ×400) revealed a large vesicular nucleus and abundant eosinophils to clear the cytoplasm. Immunohistochemical staining was positive for CD7 (b, ×400) and CD19 (c, ×400) in tumor cells, which indicated a metastasis of intrahepatic cholangiocarcinoma (ICC). These findings were similar to those of the ICC pathological specimen obtained by hepatotomy 2 years previously (d, ×400).

1c). The tumor partially invaded the bone, muscle, and dura mater. Methionine positron emission tomography (PET) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed high uptake by the skull tumors (Fig. 2) but no uptake by other lesions. Whole-body bone scintigraphy showed no uptake except by the skull.

Biopsy of the left orbital tumor for pathological diagnosis revealed a hard elastic white tumor. Histopathological examination of the tumor cells showed sheet and acinar structures. Individual cells had a large vesicular nucleus and abundant eosinophils to clear the cytoplasm (Fig. 3a). Some areas had fibroblastic and necrotic tissues. Immunohistochemical tumor cell staining was positive for CD7 and CD19 (Fig. 3b, c) and negative for CD20. These histological features indicated ICC metastasis. Because the parietal tumor showed high uptake on PET (Fig. 2b), it was diagnosed as the same metastatic tumor without biopsy. We performed stereotactic radiosurgery for both lesions. On follow-up MRI 12 months after surgery, the tumors were well controlled and symptoms improved.

Case 2: A 56-year-old female with chronic hepatitis B virus infection underwent hepatotomy for ICC. She had received preventive chemotherapy twice through an intra-arterial reservoir.

After 3 years of initial treatment, she noticed pain in the parietal region of the skull, which was found to be a slowly growing mass. Heterogenoulsy enhanced Gd-DTPA MRI showed 3 osteolytic tumors at the left parietal bone, left temporal bone, and lateral left orbit (Fig. 4), which showed heterointensity on both T_1- and T_2-weighted images. The left parietal tumor was bigger than the others and had partially invaded the intracranium in contact

with the superior sagittal sinus. PET-CT showed high uptake by the skull tumors (Fig. 5), several small lung tumors, and no uptake by other regions. These lesions were diagnosed as metastases from ICC. She received whole-brain radiotherapy (30 Gy) and tegafur, gimeracil, and oteracil potassium chemotherapy. After 1 year and 6 months, chemotherapy was considered to be ineffective and gemcitabine was administered alternatively. In the same year, the skull tumors increased and therefore stereotactic radiosurgery was performed. However, she died 4 years after the initial therapy.

Case 3: A 65-year-old male suffered from pain in the right occipital and nuchal regions. One year later, he had difficulty in swallowing and developed a hoarse voice. Neurological examination and MRI at a neighborhood hospital showed abnormalities; therefore, he came to our hospital. Physical examination showed a subcutaneous tumor in the right occipital and posterior neck regions. Neurological examination revealed hoarseness, tongue atrophy and deviation on protrusion, and atrophy of the right trapezius and sternocleidomastoid muscles. These symptoms indicated right IX, X, XI, and XIIth nerve palsy. CT showed a low-density mass at the right petrous bone, foramen magnum, and upper cervical vertebra. Mildly enhanced Gd-DTPA MRI showed hypointensity and hyperintensity on T_1- and T_2-weighted images, respectively (images not shown). Histological examination of a needle biopsy specimen showed adenocarcinoma. Whole-body CT and abdominal ultrasonography revealed a 7 × 7-cm tumor in the left liver lobe. Needle biopsy was performed, and histological diagnosis was ICC. Thus, the final diagnosis of ICC with skull metastasis was established. Conservative treatment was recommended, and he received chemotherapy and radiotherapy but died 1 year later.

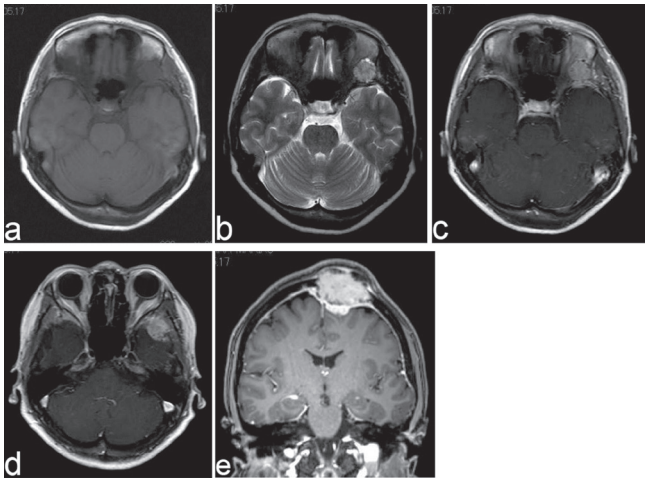

Fig. 4 Axial T_1-weighted MR image (a) showing a hypointensive lesion in the lateral left orbit, which was heterointensive on the axial T_2-weighted image (b) and enhanced heterogeneously by Gd-DTPA (c). Axial contrast-enhanced T_1-weighted image (d) showing another lesion in the left temporal bone. Coronal contrast-enhanced T_1-weighted image (e) showing a third lesion in the left parietal bone, which was bigger than the others and had partially invaded the intracranium in contact with the superior sagittal sinus. Gd-DTPA: gadolinium diethylenetriaminopentaacetic acid, MR: magnetic resonance.

Discussion

Skull metastases are the most common cranial neoplasms in adults. According to the 175-patient review of Mitsuya et al.,[9] breast cancer (54.9%) was the most common primary tumor, followed by lung cancer (14.3%), prostate cancer (6.3%), malignant lymphoma (5.1%), and others (19.4%). Reported incidence of skull metastases from hepatocellular carcinoma (HCC) is 0.4–1.6%.[5,13,16] Considering that cholangiocarcinoma accounts for only 15% of hepatic cancers[10] and ICC accounts for only 5–10% of cholangiocarcinoma,[6,11] it is obvious that the incidence of skull metastases from ICC is even more rare. In our hospital, 324 patients were diagnosed with brain or skull metastases from June 1969 to June 2011, but only 3 of them (0.9%) developed skull metastases from ICC; no patient had brain metastases from ICC. After a thorough literature search, we found only 1 case report of ICC metastasizing to the skull (Table 1).[10]

Tumors can metastasize to the skull via two pathways. One is the hematogenous pathway via the lung to the brain or skull and another is the osseous pathway via

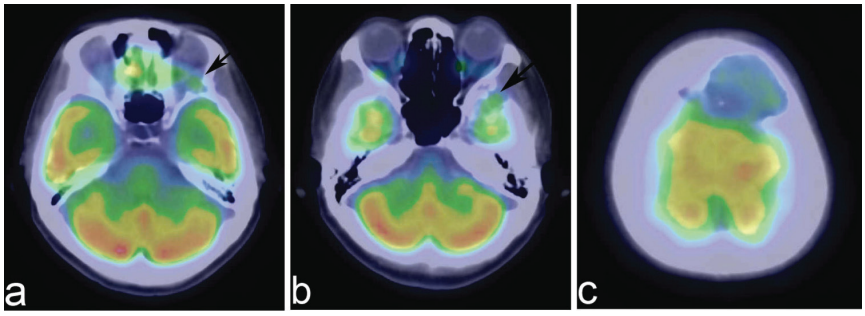

Fig. 5 PET-CT showing high uptake at the left orbital (a), left temporal (b), and left parietal (c) tumors. PET-CT: positron emission tomography computed tomography.

Table 1 Characteristics of patients with skull metastases from intrahepatic cholangiocarcinoma

Case no.	Age, Sex	Symptom	Interval	Location of skull metastasis	Metastasis to other organs	Metastasis to the brain parenchyma
1	58, F	Pain and swelling around the left eyelid	2 months	Left orbit Right parietal bone	–	–
2	56, F	Painful mass in the parietal region	3 years	Left orbit, left parietal bone, left temporal bone	Lung	–
3	65, M	Pain in the right occipital region and posterior region of the neck, Right IX X XI XII palsy	Same time	Right petrous bone Right occipital bone	Upper cervical vertebra	–
4 Miyamoto et al.[10]	67, F	Mass in the left parietal region	2 years	Left occipital bone	Th12	–

Th12: twelfth thoracic vertebra

the craniospinal system (CSVS).[15] CSVS has two main divisions: (1) the intracranial veins, which include the cortical veins, dural sinuses, cavernous sinuses, and ophthalmic veins and (2) the vertebral venous system, which includes the vertebral venous plexus (Batson's plexus).[1] This system is characterized by the lack of venous valves, which allows bidirectional blood flow.[1,2] The rise of intrathoracic or intra-abdominal pressure causes retrograde venous flow in CSVS, and the tumor cell can bypass the lungs and brain and metastasize to the skull.[1,2,15] In Table 1, the location of metastasis was along the lines of CSVS. This indicates that CSVS may be one of the metastatic pathways in skull metastasis from ICC.

Methionine-PET is a very helpful imaging method for detection of malignant tumors. Although the right parietal lesion was small and less obvious by MRI in our case 1, methionine-PET showed high uptake by the lesion. Generally, FDG-PET was less helpful than methionine-PET because of high physiological uptake by the brain parenchyma and poor localization. In several studies, PET-CT was reported to be helpful because of accurate anatomical localization of metastatic tumors in the skull base.[4] PET-CT was helpful in detecting skull base tumors in our case 2.

Metastatic skull tumors are clinically important for patients' quality of life. As is the case in brain metastasis, there are four modalities of therapy used for patients with skull metastases: surgery, irradiation, chemotherapy, and hormonal therapy.

Surgical excision is performed for a symptomatic lesion that can be removed with relative safety, low morbidity, and low mortality.[7,8,14] Although surgery improves local control and symptomatic outcome, no survival difference is observed between surgical and non-surgical groups.[3,14] Michael et al.,[8] suggested that surgery in carefully selected cancer patients provides effective palliation of symptomatic calvarial metastases that overlie or invade the venous sinuses.

Radiotherapy is performed when the lesion is difficult to resect. Therefore, it is the most common standard treatment of skull-base metastases. Laigle-Donadey et al.,[7] treated 70% of patients with skull-base metastases by radiotherapy alone or in combination with chemotherapy or surgery, and 90% were relieved of pain or cranial nerve dysfunction. Vikram and Chu[17] reported that radiation was more effective for patients presenting with symptoms of short duration. The symptomatic improvement rates were 87%, 69%, and 25% for patients with < 1 month, 1–3 months, and ≥ 3 months history, respectively. Early treatment greatly improves the chances of helping patients with skull metastases.

Radiosurgery offers an effective treatment for patients with lesions near sensitive structures or in previously irradiated fields.[9] In our cases, radiosurgery and radiotherapy had positive effects on symptom improvement and cosmetic problems.

Chemotherapy and hormonal therapy are used in combination with surgery or radiotherapy to treat systemic lesions and may produce clinical improvement.[9] However, in ICC cases, chemotherapy is controversial.[6,18]

In conclusion, the possibility of skull metastasis from ICC should be considered when patients complain of skull mass or cranial nerve palsies and skull metastasis is diagnosed. Otherwise, patients with ICC should be carefully monitored for possible development of skull metastasis.

Conflicts of Interest Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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