Cranial Metastasis as Initial Manifestation of Hepatocellular Carcinoma

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ABSTRACT

Cranial metastasis from hepatocellular carcinoma (HCC) prior to diagnosis of the primary tumor without liver dysfunction is a very rare event. Cranial metastasis may be the sole initial presentation of HCC. Early diagnosis is essential in order to treat the primary disease. Cranial metastasis from HCC should be considered in the differential diagnosis in patients with subcutaneous scalp mass and osteolytic defects on X-ray.

A 55 year old female patient without known liver disease, presented with a palpable right occipital scalp mass. On head computed tomography (CT) scan, a tumor on right orbita wall, osteolytic skull and invasion to the right frontal lobe was observed. The histological diagnosis obtained from the biopsy was a poorly differentiated cranial metastasis adenocarcinoma that was difficult to determine the origin. On positron emission tomography (PET) scan, there was a hypermetabolic mass around intra hepatal bile duct which suspicious primary cancer. The histological diagnosis obtained from the liver biopsy was appropriate with HCC grade II. The metastatic tumor was removed via occipital craniectomy. She received a palliative course of external beam radiation therapy to the right orbit. Then, she received symptomatic treatment and herbal medicine with cassava leaves for the last three months. Evaluation of bone survey shows lytic lesion at calvaria and compression fracture at vertebrae thoracal 11-12 appropriate with metastasis process. According to Barcelona Clinic Liver Cancer (BCLC) criteria she suffered from HCC terminal stage D with average survival of about 4 months.

Keywords: *hepatocellular carcinoma, cranial metastasis, palliative treatment*

ABSTRAK

Metastasis kranial dari karsinoma hepatoselular sebelum diagnosis tumor primer dengan hasil tanpa adanya gangguan fungsi hati adalah peristiwa sangat jarang ditemui. Metastasis pada tulang kranial dapat menjadi salah satu presentasi awal dari karsinoma hepatoseluler. Menegakkan diagnosis di awal sangat diperlukan untuk menentukan penatalaksanaan pada penyakit primer. Metastasis pada kranial dari karsinoma hepatoseluler harus dipertimbangkan pada kasus subkutan skalp tumor dan pada pasien dengan defek osteolitik pada gambaran radiologi.

Seorang pasien perempuan usia 55 tahun, yang tidak didapatkan riwayat penyakit hati sebelumnya, datang dengan benjolan pada region oksipital kanan. Hasil computed tomography (CT) scan kepala didapatkan tumor pada dinding orbita kanan. Dari pemeriksaan histologi menunjukkan metastasis dari adenokarsinoma berdiferensiasi buruk yang sulit ditentukan asalnya. Pada pemeriksaan positron emission tomography (PET) scan, terdapat massa hipermetabolik di sekitar duktus intrahepatik yang diduga sebagai tumor primer. Hasil biopsi menunjukkan karsinoma hepatoselular derajat 2. Dilakukan kraniektomi region oksipital pada penyebaran tumor dan dilanjutkan radioterapi paliatif pada region oksipital kanan. Selanjutnya pasien hanya mendapatkan terapi simtomatik dan daun singkong sebagai terapi herbal selama 3 bulan terakhir. Evaluasi survei tulang setelah 3 bulan menunjukkan lesi litik pada kalvaria dan fraktur kompresi pada tulang vertebrae thorakal 11-

12. Menurut kriteria Barcelona Clinic Liver Cancer (BCLC) pasien tersebut masuk ke dalam stadium terminal D dengan rata-rata angka harapan hidup 4 bulan setelah terdiagnosis.

***Kata kunci**: karsinoma hepatoseluler, metastasis kranial, terapi paliatif*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and is especially prevalent in African and East Asia.[1] The higher incidence of HCC in Asia is related to the increased prevalence of chronic viral hepatitis B.[2] Late stage HCC usually metastasizes to the regional lymph nodes and lungs, but less commonly to the skeleton.[3] HCC usually metastasizes preferentially to the vertebral column, pelvis, and ribs, but rarely to the skull.[4]

Although the incidence of bone metastases in HCC has been described as very low in autopsy studies, an increasing trend has been reported. Because of the short survival of patients with HCC, their clinical presentations were mostly concerned with the manifestations of the primary cancer itself. However, recent progress in the treatment of HCC has made it possible for the patient to survive longer, and as a result distant metastasis from HCC including bone metastasis has increased and attracted more attention than before.[4] In this report, we described a patient without previously known liver disease who presented with metastatic HCC of the skull before the diagnosis of a primary cancer.

CASE ILLUSTRATION

A 55 year old female patient presented with an incidentally found scalp mass four months prior to presentation. She did not have any history of recent head trauma or of any significant medical problems, including liver disease. She was known for having diabetes mellitus since seventeen years ago, took oral anti diabetic and insulin injection routinely. On admission, neurological and physical examination revealed no neurological deficits or hepatomegaly. A soft and non-movable mass about 1 × 2 cm over his occipital area was noted. The mass was slowly growing and caused occasional mild regional tenderness.

Laboratory tests demonstrated normal value of complete blood count, mild elevated liver function test, an alpha fetoprotein level of 14,893 ng/mL; carbohydrate antigen (CA) 19-9 386.28 U/mL and a negative serologic test for hepatitis C virus (HCV) antibody and hepatitis B virus antigen (HBsAg). Identifiable risk factors for HCC were found such as type 2 diabetes mellitus. Chest X-ray showed normal cor and pulmo.

Head computed tomography (CT) scan showed a highly enhanced extra conal lesion over right orbitae wall and enhanced right frontal lobe supra orbita which was concluded as a tumor on right orbita wall, osteolytic skull and invasion to the right frontal lobe hemangioma, meningioma, neurofibroma, sarcoma, pseudo-tumor (Figure 1). The first percutaneous needle biopsy showed group of hypercellular, pleomorphic, hyperchromatic, oval nucleus, bluish cytoplasm forming acinus with necrotic debris and eosinophilic matrix background which was concluded as adenocarcinoma.

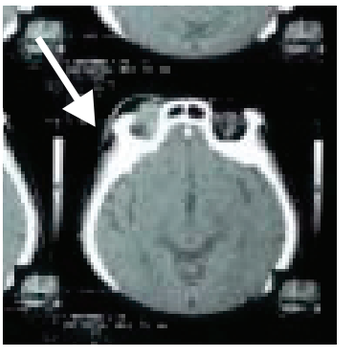

Figure 1. Head CT scan focusing on orbitae showed tumor on right orbita wall, osteolytic skull and invasion to the right frontal lobe (arrow sign)

Under general anesthesia, the tumor was radically resected along with surrounding normal bone via craniotomy. During surgery, a grossly well demarcated reddish brown mass (reflecting its high vascularity) penetrated both tables of the skull through the diploic space. The underlying duramater was intact and did not show evidence of gross tumor invasion. The second biopsy from frontal lobe of cerebri showeds tumor cranial metastasis adenocarcinoma poorly differentiated that difficult to determine the origin.

Multi slice CT (MSCT) scan post craniotomy showed solid extra axial heterogen mass in right frontal intracranial extend pass through os frontal, part of right sinus frontal, narrowing peripheral cortical sulci right frontal, without vasogenic edema. Right extraconal retroorbital space extend pass through orbital roff

destruction, with shuffled right bulbus oculi and right orbita superior musculus rectus to inferior (Figure 2).

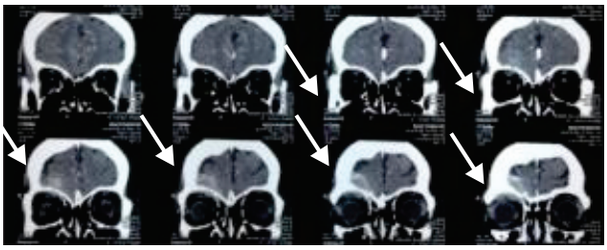

Figure 2. Multi slice head CT scan showed solid extra-axial heterogenic mass in right frontal

Retrograde diagnostic work up for detecting the primary cancer was performed. A positron emission tomography (PET) scan performed 65 minutes after Fluor-18 fluorodeoxyglucose (FDG) from head to toe; attenuated correction was performed with low dose CT non-contrast. Quantitative measurements were performed with standardize uptake value (SUV). Impression of a hypermetabolic mass around intra hepatal bile duct which was suspected to be the primary cancer (probably a cholangiocarcinoma). Hyperdense lesion with high metabolic activity in right frontal region with right frontal sinus destruction and medial wall right os orbitae with right frontal bone defect in anterior, suggesting metastasis process (Figure 3). Hypermetabolic lesion in pancreaticoduodenale lymphnode and lytic lesion left posterior os parietal suggesting metastasis process, lobulated multiple nodules in right lobe of thyroid which were very large size and metabolic activity, inhomogen density and multiple calcification.

Confirmed with liver biopsy showed billiary obstruction in liver tissue, fibrosis portal with bile duct proliferation, Tumor mass content of polygonal cells stack on solid and trabecular form, spherical/ oval nucleus, hyperchromatic, eosinophilic cytoplasm, conclusion suggestive of hepatocellular cell carcinoma grade II.

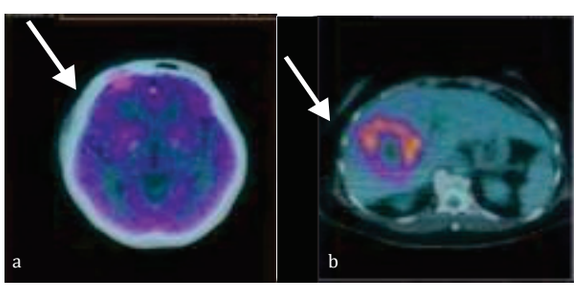

Figure 3. PET scan showed a). hyperdense lesion with high metabolic activity in right frontal region; b) hypermetabolic mass around intra hepatal bile duct

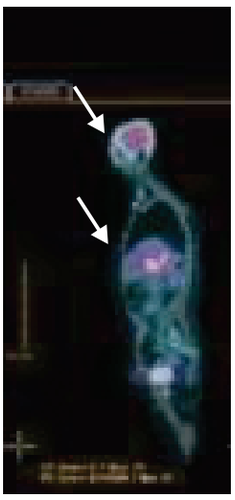

Figure 4. Positron emission tomography scan showed suspected primary cancer (cholangiocarcinoma), lesion with high metabolic activity in right frontal region suggestive metastasis process (red sign)

An abdominal sonogram identified after she underwent liver biopsy, with impressions of slightly hepatomegaly in right lobe, coarse liver texture multilobulated lobuler inhomogen right lobe liver around billiary tract, showed unclear border with diameter 3-6 cm. Close with mass area, there was spheric zone hyperechoic, clear borderline, diameter 4 x 4.5 cm. Widening right intrahepatal billiary tract, right portal vein not clearly demarcated, without ascites, suggestive malignant neoplasm with post biopsy hematoma (Figure 5).

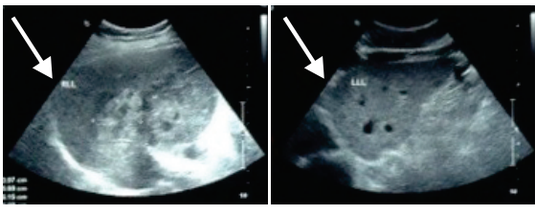

Figure 5. Abdominal ultrasonography showed multilobulated mass in homogen hyperechoic in right lobe of liver (arrow sign)

The patient received a palliative course of external beam radiation therapy to the right orbit. Intensity modulated radiation therapy (IMRT) was used to allow sparing of critical normal tissues in close proximity to the tumor. Two months after completion of IMRT to 58 Gray in 30 fractions delivered over 10 week, the patient had a complete clinical and symptomatic response. The patient was followed up in the outpatient gastroentero-hepatology clinic.

After 3 months, hepatic dysfunction due to the progression of primary cancer and evidence of the recurrence of skull metastasis were observed. She got cassava herbals medicine since the last two months.

Her abdominal USG after 1 month of therapy showeds solid mass in right liver lobe, with impressions increased size of mass and showeds peripancreatic lymphadenopathy.

The bone survey showed lytic lesion at calvaria (Figure 6), compression fracture of vertebrae thoracal 11-12 appropriate with metastasis process, spondylosis lumbalis and osteoporosis (Figure 7). She received an opioid analgetics and continued the herbal medicine.

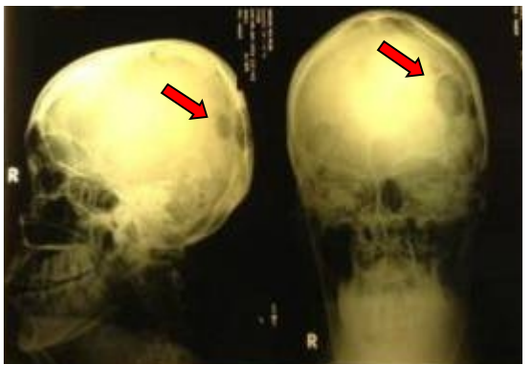

Figure 6. Skull rontgen showed lytic lesion in calvaria

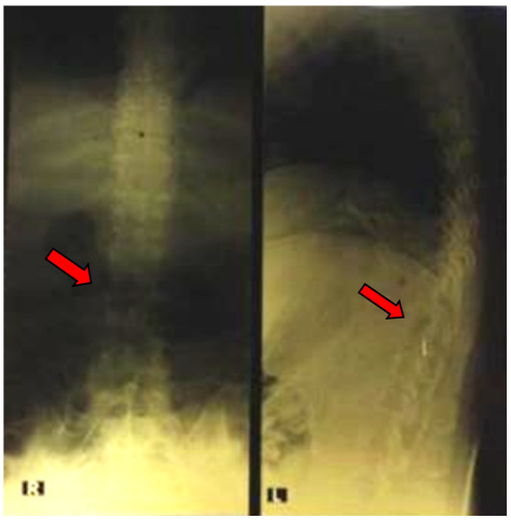

Figure 7. Thoracolumbal antero-posterior/lateral shows fracture compression at V thoracal XI-XII

DISCUSSION

The incidence of skeletal metastasis from HCC is estimated to be 2–16%, depending on the prevalence of the primary disease in the population.[4,6] The most frequent sites of osseous metastases from HCC are vertebrae, the sternum, ribs, and long bones, with the incidence in the skull is low at 0.5%–1.6%.[1,7-9] Skull metastases from HCC predominantly affect males in their sixth and seventh decades, with similar age and sex distributions to those with only HCC.[9]

In spite of the low incidence of skull metastases, there have been interesting trends in the reports about skull metastases from HCC. Moreover, in comparison with the incidence of skull metastases before the 1980's, the incidence after the 1990's has clearly increased because of a prolonged survival rate due to recent progress in the diagnosis and treatment of HCC.[4,7] Therefore, particularly in Asia, patients with HCC should be closely monitored for skull metastases. Plain skull X-ray is the most frequent initial diagnostic step in the patient with clinical suspicion of a bone lesion, while bone scan with technetium-99-methylene diphosphonate is widely used as a screening tool to detect bone metastases. On radiological examination, osteolytic type behavior with a tendency to be highly enhanced is the most common finding.[6,7] However these findings are not specific to only HCC: most skull metastases appear as osteolytic, expansile, and hypervascular lesions.[10] Metastases are the most common cranial neoplasms in adults, of which 60% are from breast and lung carcinoma, although hematogenous skull metastases can be caused by nearly all types of tumors.[11]

Because of the wide spectrum of primary cancers causing skull metastases, and because of their indistinguishable radiological findings, pathological confirmation by biopsy is required. Our case also required a biopsy for histopathological confirmation of the skull tumor. Metastases from HCC seldom emerge as an initia diagnosis of a solitary skull tumor, because skull metastasis from HCC prior to diagnosis of the primary cancer is very rare.[7] Moreover, our patient had a mildly elevated liver function test and was asymptomatic from her primary liver cancer. A solitary skull metastasis from HCC is very rare, but this type of metastases could be explained by the osseous route of HCC metastasis.

Metastases in the central nervous system from HCC generally occur through two different kinds of pathways in the advanced stage of HCC.[6,7] One of them is the hematogenous route via the lung to the brain parenchyma without skull involvement. In this group, the character of HCC is defined as a "neutrophilic" cancer, and the lung is the most common site of extracranial metastases. On the other hand, the second route is the osseous route via Batson's venous plexus to the skull. In this group, bone is the most common site of extracranial metastases, and HCC is characterized as an "osteophilic" cancer. Cancer cells might disseminate within the dipole via the diploic venous channels and expand through the inner and outer table of the skull.[7]

Therefore, it is difficult to find the skull metastasis from HCC without the presence of other bone metastases.

This patient initially visited the hospital due to the incidentally discovered scalp mass. In the literature, a subcutaneous mass with occasional pain is the most common clinical presentation (63%), followed by neurological deficits (44%), headache (11%), and seizure.[1] The neurological deficits, such as facial palsy, deafness, visual disturbance, facial numbness, weakness of limbs, and other cranial nerve palsies, are associated with the tumor size and location. Neurological deficits are more frequently present in metastases of the skull base rather than the cranial vault.[1,10]

Several treatment options can be used to treat the skull metastases from HCC, including direct ethanol injection therapy, radiotherapy, surgical resection, herbal medicine, stem cell therapy and supportive management. Many previous reports suggested that most patients with skull metastases died due to liver failure and that surgical resection of the metastatic lesion could not prolong survival.[1,4,10] The stage of the primary cancer is mostly associated with the prognosis. However, surgical resection of the skull metastases is acceptable for preventing intracranial hemorrhage and neurological deterioration. Surgical intervention also allows biopsy, whereby the tumor can be histologically confirmed; such biopsies are easier to perform in cranial vault-sited cases.[1,3,12]

The present study examined apoptotic inducing mechanisms in the natural killer (NK) cell cytotoxic activity pathway to determine an additional measurement for NK cell effector function. The results showed that perforin was significantly correlated with cytotoxic activity and degranulation, indicating that it may be an additional measurement for NK cell cytotoxic activity.

The correlation of perforin release with the lysis of tumour cells and degranulation suggests that perforin may be an additional measurement for NK cell effector function. As perforin is a lytic protein released from NK cells to induce apoptosis in the target cell, measurement of perforin may be beneficial in the clinical setting for identifying deficiencies affecting cytotoxic activity.

Although a solitary skull metastasis prior to the diagnosis of HCC demonstrates rare metastatic behavior for HCC, especially in Asia, skull metastases from HCC should be included in the differential diagnosis of skull tumors, even if the patient is asymptomatic of liver cirrhosis. With the increase survival of HCC patients, clinically significant bone metastases have also increased, affecting the patients' quality of life. Therefore, early diagnosis and proper management of bone metastasis from HCC is essential to prevent deterioration in the quality of life of HCC patients.

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