A Metastatic Hepatocellular Carcinoma Manifested as Cerebellar Hemorrhage

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Spontaneous cerebellar hemorrhage is an uncommon manifestation of metastatic hepatocellular carcinoma (HCC) in the central nervous system. A 52-year-old man with a 45-month history of HCC presented with sudden onset of severe vomiting, headache and difficulty walking. A preliminary diagnosis of hypertensive intracerebellar hemorrhage was made when he was admitted to the intensive care unit. The patient underwent a suboccipital craniotomy to evacuate the intracranial cerebellar hematoma. After a period of treatment, he was discharged from hospital. However, the patient's condition began to worsen six months after the operation. Magnetic resonance imaging of the brain documented a mass in the right hemisphere of the cerebellum. The tumor was radically resected and histology was consistent with metastatic HCC. After one year of regular rehabilitation, the patient could walk with a walker but required supervision and was partially dependent on family members for daily activities. **(Mid Taiwan J Med 2008;13:58-63)**

Key words

Cerebellar hemorrhage, Hepatocellular carcinoma, Metastatic

INTRODUCTION

The primary cause of cerebellar hemorrhage is hypertension. The initial symptoms are sudden onset of headache, dizziness, and vomiting. Other causes include medications (anti-coagulants, and sympathomimetic drugs), arteriovenous malformation and tumor-related hemorrhage. The most common primary origins of brain metastases are lung, breast carcinoma, and melanoma [1]. Approximately three-quarters of metastases to the brain occur in the cerebral hemisphere, and one-quarter of those occur in the cerebellum. Most cerebellar tumors are metastatic in origin. Approximately 64% of hepatocellular carcinomas (HCC) metastasize to other sites. Hepatocellular carcinoma commonly metastasizes to the lung, regional lymph nodes and adrenal glands, but rarely to the brain. Shuangshoti et al [2] and Qureshi et al [3] reported that hepatic tumor metastases to the brain account for 1.3% to 2.9% of all metastatic brain tumors. Metastatic HCC to the cerebellum manifesting as hemorrhage is rare; therefore, we present this report to alert physicians to the possibility of metastatic tumors in the cerebellum in patients with HCC.

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CASE REPORT

A 52-year-old man presented to the emergency department with sudden onset of severe nausea and vomiting and persistent occipital headache. The patient appeared acutely ill but was alert and well oriented. He walked with a broad-based gait with trunk swaying to the right side and demonstrated poor sitting

balance. He had no history of diabetes mellitus, hypertension, family history of hepatocellular carcinoma, or smoking. He rarely drank alcohol and did not abuse intravenous drugs. He was a hepatitis B surface antigen (HbsAg) carrier and had been well until approximately 68 months prior to this admission when one nodule was noted on Chest X-ray. He refused to undergo any invasive procedures at that time. The nodule was monitored at regular follow-ups and a diagnosis of HCC was made 45 months prior to this admission. Computed tomography of the abdomen showed a 7-cm well-enhanced mass in the right lower lobe of liver. He underwent segmentectomy of the liver and transcatheter hepatic artery embolization followed by pure ethanol injection in another hospital 45 months prior to this admission. The patient was regularly followed and his liver biochemical tests were normal.

When he presented to the emergency department, his temperature was 36.5°C, blood pressure was 143/87 mmHg, pulse was 58 beats per minute and oxygen saturation was 100 percent. On physical examination, there were no signs of trauma to the face or scalp. An examination of the chest, heart, and abdomen disclosed no abnormalities. The patient's arms and legs were well perfused with normal pulses. On neurologic examination, the pupils were 2.5 mm in diameter, equal, round, and reactive to light. Bilateral corneal reflexes were present, and his face was symmetric. Muscle strength was grade 4 in the right upper and lower limbs. Deep tendon reflexes were normal, as was sensation. Laboratory studies revealed alanine transaminase (ALT): 23 IU/L; aspartate transaminase (AST): 36 IU/L. Chest radiography showed multiple fine reticular nodules in both lungs and one nodular lesion in the lower lobe of the left lung. Computed tomography (CT) of brain revealed a highly dense lesion in the right cerebellar hemisphere with rupture to the 4th ventricle but no mass effect (Fig. 1A). The preliminary diagnosis was cerebellar hemorrhage; he was admitted for further treatment on the same day.

The patient underwent a suboccitital craniotomy to evacuate the intracranial cerebellar hematoma on the admission day; however, no specimen was sent to the pathologist for further examination at that time. Laboratory studies at two-month follow-up revealed ALT: 48 IU/L; AST: 34 IU/L; α-fetoprotein (AFP) (enzyme immunoassay, EIA): 0.735 ng/m L. After three months of rehabilitation, he could walk with a walker under supervision. He was regularly followed at his neurosurgeon's clinic.

The patient's headaches, dizziness and

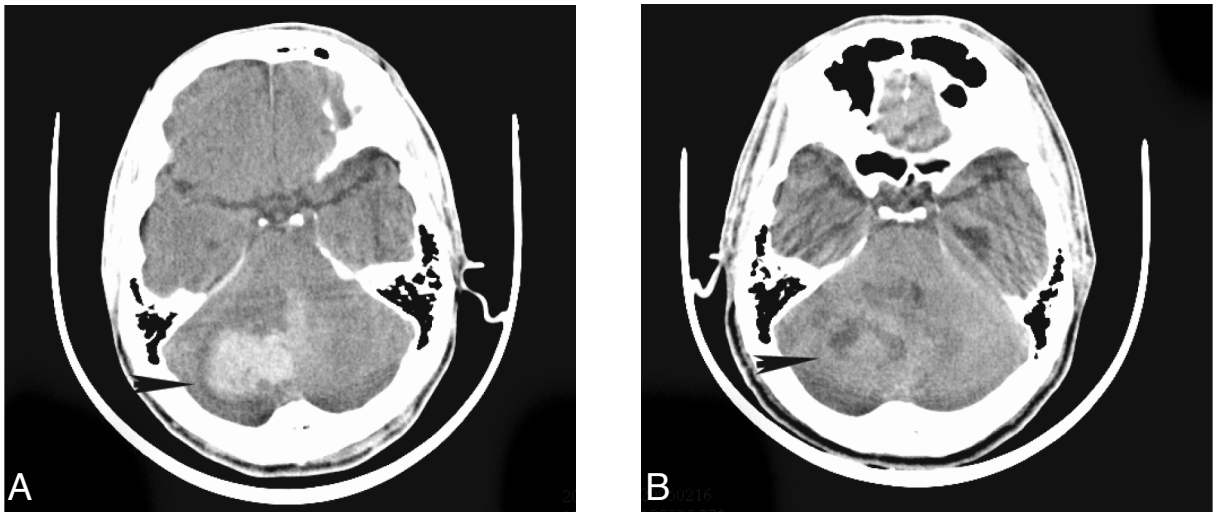

Fig. 1. Brain CT scan before surgery (A) reveals a high density lesion in the right cerebellar hemisphere. The residual hematoma in the right cerebellar hemisphere (B) appears iso- to hypodense on brain CT at 6-mo follow-up.

difficulty walking progressively worsened during the 6 months of postoperative follow-up. Physical examination at 6-month follow-up demonstrated a wide-based ataxic gait but no focal or bilateral weakness or coma; the patient had intact cognition, strength, deep tendon reflexes, and sensation in all four extremities.

Computed tomography (CT) of brain at 6-month postoperative follow-up showed that the residual hematoma in the cerebellum vermis was isodense to hypodense with compression of the 4th ventricle and obstructive hydrocephalus (Fig. 1B). Magnetic resonance imaging (MRI) of the brain demonstrated a mass in the right cerebellar hemisphere (Fig. 2). Laboratory studies revealed AFP: 1.17 ng/mL, carcinoembryonic antigen (CEA): 0.57 ng/mL, cancer antigen 15-3 (CA15-3): 14.2 U/mL, prostatic acid phosphatase (PSA): 0.863 ng/mL, ferritin: 133 ng/mL, cancer antigen-125 (CA-125): 5.65 U/mL, carbohydrate antigen 19-9 (CA19-9): 16.1 U/mL, squamous cell carcinoma associated antigen (SCC): 0.5 ng/mL, hepatitis B surface antigen (HbsAg): negative, antibody to hepatitis B surface antigen (Anti-HBs): 1.7, IgG antibody subclass of antibody to hepatitis B core antigen (Anti-HBc-IgG): positive, and antibody to hepatitis C virus (HCV Ab): negative. Abdominal sonography revealed no focal solid organic lesions and no recurrent tumors in the liver. Chest radiography and CT of chest revealed multiple nodules in both lungs. The largest two were in the upper lobes of the right lung and lower lobe of the left lung; images also demonstrated enlarged lymph nodes in the right axilla. No definite hypodense lesions were noted in the liver.

The cerebellar tumor was radically resected via a posterior suboccipital craniectomy. Histology demonstrated epitheloid and polygonal tumor cells arranged in a trabecular pattern with clear cytoplasm. Focal tumor necrosis was noted as well. Immunohistochemistry was negative for cytokeratin (CK) and glial fibrillary acidic protein (GFAP) and positive for CK8, a profile consistent with metastatic hepatocellular carcinoma (Fig. 3). The patient was discharged home on postoperative day 16.

Six months after the second operation, the patient presented with ataxic dysarthria and truncal ataxia with broad-base stance and gait, but was otherwise doing well. He could walk with a walker under supervision and needed moderate assistance in all activities of daily living. Chest radiography showed several nodules in both lungs and a 52-mm mass in the upper lobe of the right lung near the mediastinum. The patient has refused to undergo bronchoscopy or chemotherapy for his lung tumor.

DISCUSSION

In this case, a diagnosis of hypertensive intracerebellar hemorrhage was made after the

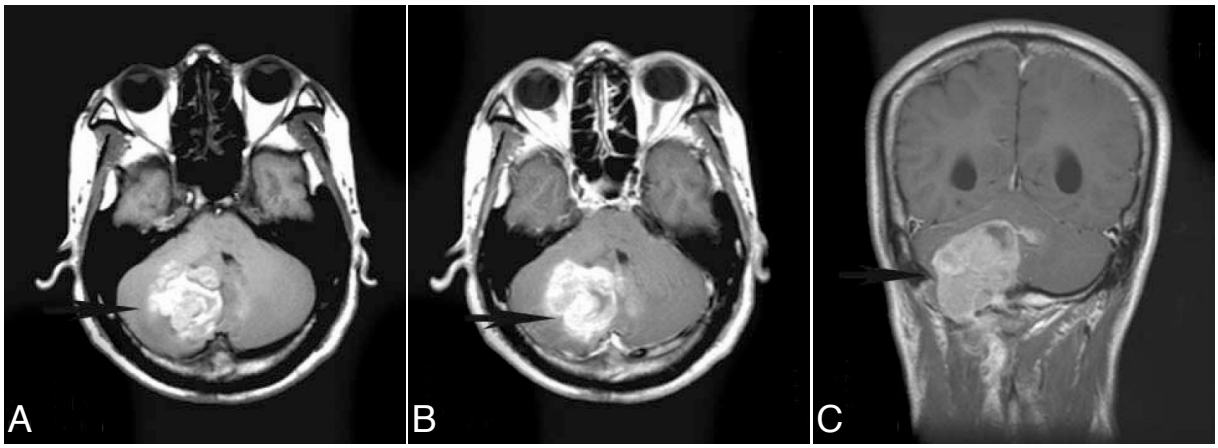

Fig. 2. Noncontrast axial T1-weighted MRI of the brain (A) demonstrates heterogenous high signal intensity in the right cerebellum. Postcontrast axial T1-weighted MRI (B) shows the new enhanced area. Coronal T1-weighted MRI with contrast (C) shows tumor with skull base invasion and downward extension to upper neck.

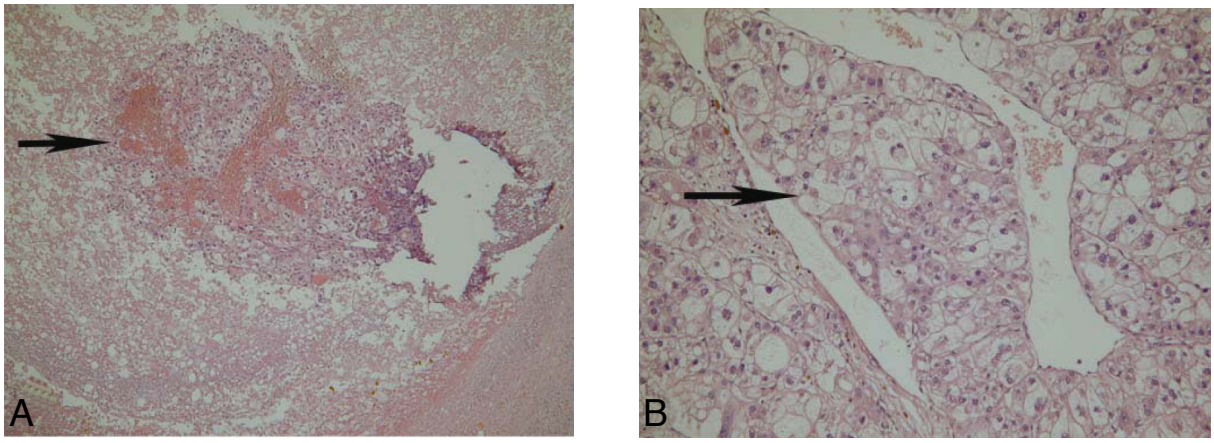

Fig. 3. Photomicrographs demonstrate the histological features of cerebellar lesion. Panel A shows focal tumor necrosis (H & E, original magnification ×40). Panel B shows epitheloid and polygonal tumor cells with clear cytoplasm, arranged in a trabecular pattern (H & E, original magnification ×200).

cerebellar hematoma had been removed. No specimen was sent to the pathologist for further examination. After participating in regular and comprehensive rehabilitation programs, the patient still required minimal assistance in all activities of daily living after he was discharged home. Six months after the operation, the patient presented with progressively worsening ability to walk. Recurrent cerebrovascular disease was preliminarily diagnosed. Computed tomography of the brain showed that the residual hematoma in the cerebellar vermis was isodense to hypodense with compression of the 4th ventricle, which induced obstructive hydrocephalus. This was an unexpected finding because the hematoma should have been completely reabsorbed, and should have presented as a linear low density lesion with peripheral brain tissue atrophy. Since there was a tumor-like mass noted in the chest at the emergency department, an underlying cause including primary or metastatic tumor should have been considered. Magnetic resonance imaging of the brain confirmed a mass in the right cerebellum seven days later. The tumor was resected and the finding supported the hepatocellular origin of the tumor.

Intracerebral hemorrhage (ICH) is classified as primary or secondary, depending on the underlying cause of hemorrhage. Primary ICH refers to a hemorrhage that originates from spontaneous rupture of small arteries or arterioles that have been damaged by chronic hypertension or amyloid angiopathy. Secondary ICH refers to hemorrhage resulting from trauma, arteriovenous malformation, intracranial aneurysm, coagulopathy, haemorrhagic conversion of cerebral infarct, dural sinus thrombosis, intracranial neoplasm, cavernous angioma, dural arteriovenous fistula, venous angioma, cocaine or sympathomimetic drug exposure or CNS vasculitis. [3] Hypertension is the most important and prevalent risk factor, directly accounting for about 60% to 70% of cases [4,5]. The second most common cause of primary ICH is cerebral amyloid angiopathy, which accounts for about 15% of cases [3]. The most common sites of primary ICH are the basal ganglia, deep cerebellum and pons. When hemorrhages occur in other brain areas or in nonhypertensive patients, greater consideration should be given to head injury, bleeding disorders, anticoagulant therapy, neoplasms, and vascular malformations. For the severely hypertensive patient with a well circumscribed and homogeneous hematoma located in a typical location for hypertensive ICH, the clinician can regard hypertensive hemorrhage as the first differential diagnosis. Evaluation for a bleeding disorder should be performed in every patient with an ICH. Hemorrhage is more common in metastatic than in primary brain tumors, and tumor-related hemorrhage is the most common cause of brain hemorrhage in patients

with systemic solid tumors [6]. Brain metastases are the most common cerebral tumors. The most common primary site of origin is lung; skin, kidney, and breast account for much of the remainder [1]. Most metastases occur at the junction between gray and white matter in the cerebral hemispheres, but deeper supratentorial locations are also common; fewer occur in the cerebellum or brain stem [7].

Hepatocellular carcinoma is the fifth most common cancer and the third leading cause of cancer-related mortality worldwide [8]. The higher incidence of HCC in Asia is linked to the increased prevalence of chronic viral hepatitis. HCC metastasizes by hematogenous and lymphatic routes [9]. Shee-Chan Lin et al [10] reported that manipulation of tumor with transcatheter arterial embolization will increase the risk of hematogenous metastasis due to an increase in activity of serum type IV collagen-degrading enzyme, or a decrease in activity of the tumor invasion-inhibitor factor [11]. HCC commonly metastasizes to the lung, regional lymph nodes and adrenal glands, but rarely to brain. In HCC and other carcinomas, seeding of the brain, the meninges, or the cranium is usually in the distribution of the middle cerebral artery [9].

If there is no known cancer and intratumoral hemorrhage is suspected, resection or biopsy of the hematoma should be performed. Careful neuropathologic examination is required, because the tumor can be microscopic. Factors affecting the prognosis of patients with metastatic brain tumor include age, primary tumor site, pretreatment performance status, presence of extracranial disease, interval between treatment of the primary lesion and of brain metastasis, number and location of intracranial metastases as well as surgical excision of brain metastasis [12]. Hypertension is the most important and prevalent risk factor, directly accounting for about 60% to 70% of intracerebral hemorrhage [4,5]. It is easy for the clinician to ignore tumor-related hemorrhage. Brain metastases, but especially cerebellar metastases, from hepatocellular carcinoma are rare. In conclusion, this report should alert the physician to the possibility of cerebellar metastasis in patients with HCC.

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轉移性肝細胞癌以小腦出血為初始表現

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小腦出血的原因以高血壓爲主，初始症狀通常是突然急遽頭痛，眩暈及嘔吐。其他原因，包括使用藥物(如抗凝血劑，交感神經刺激劑)，動靜脈畸形破裂，以及腫瘤出血等雖有零星病例報告，但案例甚少。腦部轉移性腫瘤多源至肺癌，乳癌，和黑色素瘤，其中約有四分之三轉移到大腦半球，四分之一轉移到小腦。小腦最常見的腫瘤是轉移性腫瘤。肝細胞癌會有64%的肝外轉移，主要以肺部，局部淋巴結及腎上腺爲主。肝細胞癌轉移至腦部，並以小腦出血之病例則非常罕見。本文報告一位52歲男性有B型肝炎帶原病史患者，於六年前在他院門診無意中發現肺部有結節，但未做後續追蹤治療。五年前在接受肝癌篩檢時發現有肝細胞癌而接受肝栓塞及手術治療。後續門診追蹤數年並無肝細胞癌復發的現象。首次於本院住院乃因突然急遽頭痛，眩暈，全身無力，口齒不清，無法走路和嚴重嘔吐送至急診。腦部電腦斷層發現小腦出血，懷疑是高血壓性小腦出血遂施行手術移除血塊，患者情況穩定後，即轉至復健科病房接受復健治療。出院後六個月於神經外科門診追蹤時，因病患再度主訴有頭痛，眩暈及步態更不穩的現象而安排腦部電腦斷層後，才高度懷疑是小腦腫瘤。一週後的腦部磁振造影證實是小腦腫瘤。經腦部手術切除後病理檢查證實爲轉移性肝細胞癌。透過此罕見病例，我們必須謹記小腦出血的各種可能，隨時保持警覺，如果患者合併肝癌病史時，要考慮是否有遠處轉移的可能性。（**中台灣醫誌 2008;13:58-63**）

關鍵詞

小腦出血、肝細胞癌、轉移性

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