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Clinical Features of Liver Cancer with Cerebral Hemorrhage

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Background: Cerebral hemorrhage is common in patients with cancer, but the clinical features and pathogenesis of liver cancer patients with cerebral hemorrhage are not well known.

Material/Methods: Liver cancer patients who developed cerebral hemorrhage were recruited from the First Affiliated Hospital of Guangxi Medical University between January 2003 and December 2014. We retrospectively analyzed clinical presentations, results of laboratory tests, and imaging examinations. The clinical features and pathogenesis were summarized.

Results: Among 11133 patients with liver cancer, 9 patients (0.08%), including 3 females and 6 males met the inclusion criteria. The age range was 48–73 years and the average age was 61.67±8.97 years. Five patients did not have traditional hemorrhage risk factors and 4s had the risk factors; however, all had developed hepatocellular carcinoma, and 3 had developed metastasis. All 9 patients showed elevated tumor markers: an increased AFP level was detected in 6 patients, coagulation dysfunctions in 8 patients, and abnormal liver functions in 6 patients. Five patients had developed cerebral hemorrhagic lesions in the lobes of their brains, while hemorrhagic lesions in the basal ganglia occurred in 3 patients and in the brainstem in only 1 patient. Four patients had clear consciousness, while 5 patients were in coma and showed poor prognosis.

Conclusions: Patients who have liver cancer complicated with cerebral hemorrhage usually lack traditional risk factors of cerebral hemorrhage. The site of cerebral hemorrhage is often detected in the lobes of the brain. Coagulation dysfunctions might be the main pathogenesis of liver cancer complicated with cerebral hemorrhage.

MeSH Keywords: Carcinoma, Hepatocellular • Cerebral Hemorrhage • Neovascularization, Pathologic

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Background

Cerebral hemorrhage is a common complication of cancer [1,2]. Recent studies showed that the risk of cerebral hemorrhage is quite high in cancer patients [3[, indicating that cancer itself can directly or indirectly lead to the development of cerebral hemorrhage; therefore, we define this complication as cancer-related cerebral hemorrhage [4,5]. Furthermore, recent evidence shows that hypertension is rare in patients with cancer-related cerebral hemorrhage. Cerebral hemorrhage is usually caused when bleeding develops in the brain tumor due to metastatic cancer, cancer-related coagulation disorders, and adverse effects of cancer-related treatments [4,6–8]. However, there are complicated situations, such as the development of different cell types, their growth phases, and intracranial metastasis; these complications might enhance the manifestation of a variety of clinical features of cancer, including cerebral hemorrhage [9,10].

Liver cancer is a common malignancy with poor prognosis. It is the sixth most commonly occurring cancer in the world and the third most frequent cause of cancer mortality [11]. The highest incidence rates of liver cancer have been reported in Asia and Africa. Approximately 85% of all liver cancers occur in these areas [12]. Metastases of liver cancer are common; however, there are rare cases in which patients develop brain metastases from hepatocellular carcinoma. It is noteworthy that patients with liver cancer can also develop complications of cerebral hemorrhage [3,13–16] or hematomas [17]. On some occasions, intracerebral hemorrhage is the first presentation of brain metastatic primary clear cell carcinoma of the liver [18,19]. However, to date, no study has reported clinical features and potential pathogeneses of liver cancer accompanied by cerebral hemorrhage as a complication. The incidence of liver cancer is quite high in Guangxi Province, China, with a liver cancer mortality rate of 34.4/10 million in 2004–2005. Liver cancer has become the leading cause of cancer-related deaths in Guangxi and seriously endangered the health of local people (20). In the present study, our aim was to study the clinical features of liver cancer patients with cerebral hemorrhage in Guangxi. At the First Affiliated Hospital of Guangxi Medical University, between January 2003 and December 2014 we collected clinical data from liver cancer patients who also had the complication of cerebral hemorrhage. Furthermore, we retrospectively analyzed the clinical features of hepatic cancer patients with cerebral hemorrhage in order to improve our understanding of liver cancer.

Material and Methods

Diagnosis: Inclusion and exclusion criteria

Diagnostic criteria

Cases were selected according to the ICD-10 standard, which is a component of an international statistical classification of diseases. In total, we recruited 11 133 liver cancer patients from the database. We obtained the data of liver cancer patients using the code C22. Thus, we searched for the data of liver cancer patients, whose condition was complicated with cerebral hemorrhage. For this purpose, we used the coding C22 and I61. The diagnostic criteria for cerebral hemorrhage are referred as the 2007 Guidelines for the Diagnosis and Treatment from the American Heart Association [21]. The diagnosis of primary liver cancer was made according to the guidelines set by Giammarile et al. in France [22]. The approval for medical ethics of this study was obtained from the Human Ethics Committee at our hospital.

Inclusion criteria

Liver cancer was confirmed only by pathological diagnosis; we did not check whether each of the liver cancer cases met the criteria of clinical treatment of liver cancer. We confirmed the recurrence and metastasis of liver cancer in some cases. While treating liver cancer patients in the hospital, we came across patients with local neurological deficiency, such as sudden headache, limb weakness, numbness, and unclear speech. By performing brain CT or MRI scan and susceptibility-weighted imaging (SWI), we confirmed the presence of intracranial hemorrhage in these patients. Intracranial hemorrhage was diagnosed in the initial stages in these patients. These patients developed neurological symptoms due to intracranial hemorrhage. We hospitalized the patients who had developed intracranial hemorrhage. Then, we diagnosed liver cancer in these patients for the first time. A panel of an oncologist, neurologist, and neuroimaging experts worked together to recruit patients in this study.

Exclusion criteria

We excluded patients who developed cancer in other systems of the human body. We also excluded patients who developed the complication of cerebral infarction. We excluded liver cancer patients who had developed cerebral hemorrhage after 5 years of diagnosis. We did not find any patients showing evidence of recurrence or metastasis of non-active liver cancer. Finally, we excluded patients that did not have sufficient clinical data.

Collection of clinical materials

We collected the following data: demographic characteristics, including age and sex; traditional risk factors such as diabetes,

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hypertension, high cholesterol, and stroke; liver cancer-related data such as pathological types of cancer cells and metastasis; and treatment methods. We also included the following data related to acute cerebral hemorrhage: main symptoms, signs, severity of neurological functions, and consciousness. The National Institute of Health Stroke Scale (NIHSS) was used for evaluating the severity of neurological functions. The Glasgow coma scale (GCS) was used to evaluate the level of consciousness. To reduce the effect of progression of liver cancer on physical activities of patients, we included a modified Rankin scale (mRS) and evaluated the prognosis of patients at 30 days after they had been diagnosed with cerebral hemorrhage. mRS scores >3 indicated poor prognosis. We collected the results of routine blood tests, blood biochemistry tests, coagulation indexes, D-dimer, tumor markers, electrocardiography (ECG), cardiac color Doppler ultrasound, cervical blood Doppler, CT angiography (CTA), brain CT, brain magnetic resonance image (MRI), and magnetic resonance angiography (MRA). According to a research study conducted by Navi et al., [7] on cerebral hemorrhage, coagulation dysfunctions were present in the patient if any of the parameters met the following criteria: platelet $<100\times10^9$/L, International Normalized Ratio (INR) >1.5, activated partial thromboplastin time (APTT) >45 s, prothrombin time (PT) >15s, disseminated intravascular coagulation (DIC): fibronectin <2 g/L, and D-dimer >290 ng/dL.

Results

In the present study, we selected a total of 11 133 patients with liver cancer. Among them, there were 9 patients (0.08%) who met the criteria for liver cancer and cerebral hemorrhage, including 3 females and 6 males, with an age range of 48–73 years. The average age of these patients was in the range of 61.67±8.97 years. We diagnosed liver cancer in all 9 patients. Among them, 3 patients had developed metastasis in the lymph nodes of their armpit, and they had also developed secondary metastasis in the distant tissues from the primary liver and lungs tumors. Interestingly, no metastasis had developed in the brain before the development of cerebral hemorrhage, which seemed to be a complication of liver cancer. According to blood biochemistry tests, 6 patients had abnormal liver function. Furthermore, coagulation dysfunction was detected in 8 patients, including 1 with disseminated intravascular coagulation (DIC). Nine had elevated tumor markers, 6 had increased alpha-fetoprotein (AFP) level, 5 had increased cancer antigen (CA125) level, 5 had elevated CA199 level, 3 had increased CA153 level, and 4 had elevated levels of carcinoembryonic antigen (CEA).

According to the results of hepatic cancer treatment, there were 2 patients who received hepatectomy and chemotherapy. Furthermore, 1 patient received simple chemotherapy, while the remaining patients did not continue with cancer treatments (Table 1).

Among the 9 patients recruited in this study, 4 (44.44%) had a history of hypertension. The remaining 5 had no traditional stroke risk factors such as hypertension, high cholesterol, diabetes, smoking, or drinking history. The onset of cerebral hemorrhage was characterized by the following symptoms: acute clinical presentation such as sudden headache, disturbance of consciousness, limb weakness, and unclear speech. Cerebral hemorrhage developed in 4 patients receiving treatment for liver cancer; 1 developed cerebral hemorrhage at 1 month after the diagnosis of liver cancer, and 3 developed cerebral hemorrhage after approximately 1 year (11, 12, and 13months) after being diagnosed with liver cancer. The remaining 5 were hospitalized when they developed cerebral hemorrhage. Liver cancer was subsequently detected for the first time in these 5 patients. Most hemorrhages occurred in the cerebral area (5 patients) (Figure 1); however, there were 3 patients that developed hemorrhage in the basal ganglion. Furthermore, we found only 1 patient who developed hemorrhage in the brain stem. All 5 patients with cerebral hemorrhage became comatose, with coma severity in the range of 5–8 on the GCS. According to the NIHSS, the scores were in the range of 1–4 in 4 patients with full consciousness. Twenty-one days after the patients had cerebral hemorrhage, we again performed brain CT and confirmed that lesion signals within the brain were consistent with cerebral hemorrhage-related changes. Moreover, we did not observe any intracerebral tumor or cerebral metastasis in patients with liver cancer. None of the patients received anti-platelet or anti-coagulation treatments. All the patients received conservative treatment, but in 1 patient we performed drilling drainage. Thirty days after cerebral hemorrhage, mRS was in the range 0–4 in 4 patients and 6 in 1 patient, who died. The results are summarized in Table 2.

Discussion

Clinical features of liver cancer complicated with cerebral hemorrhage

In the present study, only 0.08% of liver cancer patients developed cerebral hemorrhage despite receiving treatment for liver cancer at the hospital. In all these patients, cerebral hemorrhage developed approximately 1 year (365 days) after their diagnosis of liver cancer was confirmed. The correlation of timing between the occurrence of cerebral hemorrhage and the diagnosis of liver cancer was roughly consistent, indicating that the occurrence of cerebral hemorrhage in liver cancer patients should have the same features of occurrence as other types of cancer. It is worth noting that 5 patients were hospitalized and treated for cerebral hemorrhage; in these patients, liver cancer was diagnosed for the first time during their course of treatment. This indicates that cerebral hemorrhage is the first manifestation of symptoms in some patients with liver cancer.

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Table 1. Clinical materials of 9 patients.

Number	Gender	Age	Types of tumor	Metastasis	Cancer treatment prior to cerebral hemorhage	Blood tests	Coagulation functions	Liver function tests	Tumor markers
1	Male	70	Hepatic cancer	No	Give up	PLT 37×10^9	APTT 44.9 PT 21.92 TT 9.27 INR 2.26 FIB 6.33 D-dimer 83.30	ALT 51 AST 163 ALB 23.7 TBil 112.4 DBil 50.8	AFP: 5.15 CA125 352.6 CA153 42.10 CA199 1132 CEA 5.01
2	Male	48	Hepatic cancer	No	Surgery + chemo-therapy[a]	PLT 228×10^9	APTT50 PT 15.6 TT >120 INR 1.04 FIB3.44 D-dimer 226.14	ALT 109 AST 77.00 TP 71.0 TBil 13.4 DBil 20.2 ALB 36.00	AFP 12.72 CA125 154.47 CA153 13.24 CEA 7.32
3	Female	51	Hepatic cancer	Metas-tasis of lymph nodes of armpit	Give up	PLT 262.4×10^9	APTT48.2 PT26.8 TT 2.78 INR 0.9 FIB7.02 D-dimer 30.82	ALT 8 AST 17 T P67.5 TBil 10.3 DBil 4.2 Alb 37.9	AFP 6.54 CA199 21.11 CA125 15.07 CA153 178.25
4	Male	65	Hepatic cancer	Metas-tasis within the liver	Give up	PLT 353×10^9	APTT 32.2 PT 10.8 TT 5.6 INR0.75 FIB 3.43 D-dimer 107.04	ALT 66 AST 89 TP63.3 TBil 47.5 DBil 20.2 ALB 26.2	AFP 3000 CA125 143.13 CA153 21.0544 CA199 26.01 CEA 0.42
5	Male	57	Hepatic cancer	No	Give up	PLT 144×10^9	APTT50.2 PT 19.08 TT 12 INR 1.28 FIB 2.68 D-dimer 112.44	ALT 37 AST 63 TP 60.3 TBil 12.4 DBil 5.6 ALB34	AFP 46.6 CA125 114.03 CA153 19.05 CA199 46.93 CEA 3.45
6	Male	56	Hepatic cancer	Lung	Chemo-therapy[b]	PLT 19×10^9	APTT 48.9 PT 30.64 TT 11.2 INR 1.89 FIB 1.4 D-dimer 1283.57	ALT 44 AST 191 TP 79 Tbil 365 Dbil 187.6 ALB 22	CA125 >600 CA153 34.2 CA199 341.15 AFP >35350
7	Female	70	Hepatic cancer	No	Surgery + Chemo-therapy[c]	PLT 222×10^9	APTT54.9 PT 24.95 TT 9.78 INR 1.06 FIB 5.12 D-dimer 34.37	ALT 21 AST 36 TP 75 TBil 20.3 DBil 5.0 ALB28	AFP 21.6 CA125 106.03 CA153 19.95 CA199 46.93 CEA 3.45
8	Female	73	Hepatic cancer	No	Give up	PLT 143.6×10^9	APTT 42.8 PT 34.85 TT 7.8 INR3.36 FIB 5.19 D-dimer 56.16	AST 36 ALT 17.9 TP 68 TBil 18.9 Dbil 3.7 ALB 39	AFP 1898 CA125 829.58 CA153 21.07 CA199 38.16 CEA 5.15

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Table 1 continued. Clinical materials of 9 patients.

Number	Gender	Age	Types of tumor	Metastasis	Cancer treatment prior to cerebral hemorhage	Blood tests	Coagulation functions	Liver function tests	Tumor markers
9	Male	65	Hepatic cancer	No	Give up	PLT 147×10^9	APTT 34.9 PT 26.95 TT 10.45 INR3.47 FIB 3.51 D-dimer 322.02	AST 57 ALT 19 TP 81 TBil 18.9 Dbil 97.7 ALB 31.8	AFP 6.85 CA125 165.58 CA153 19.12 CA199 1.46 CEA 5.79

NB – [a] fluorouracil; Cisplatin; [b] fluorouracil, Gemcitabine, mitomycin C; [c] fluorouracil, Epirubicin, interferon. PLT – platelet (100~300×10^9/L); APTT – activated partial thromboplastin time (23~45 s); PT – Prothrombin time (9~15 s); TT – thrombin time (9~154s); D-dimer (<290 ng/dL); INR – International Normalized Ratio (0.8~1.4); FIB – fibrinogen (2~5 g/L); TBil – total bilirubintotal bilirubin (3~22 μmol/L); DBil – direct bilirubin (0~6 μmol/L); TP – total protein (60~83 g/L); ALB – albumin (35~55 g/L); AST – glutamic-oxalacetic transaminase (8~45 U/L); ALT – glutamic-pyruvic transaminase (5~40 U/L); AFP – alpha-fetoprotein (0~7 ng/ml); CA – cancer antigen: CA125: (0~35 U/ml); CA199: (0~27 U/ml), CA153: (0~25 U/ml); CEA – carcinoembryonic antigen (0~5 ng/ml).

This is in good agreement with previous reports establishing that cerebral infarction is the first manifestation of liver cancer in some patients [23–25]. However, cerebral hemorrhage is the first manifestation in a very few liver cancer patients.

Cerebral hemorrhage is one of the complications of the central nervous system in patients with liver cancer. However, it is worth exploring whether cancer increases the risks of cerebral hemorrhage. In 2012, Zöller et al. [5] collected cancer data between from 1987 to 2008 in Sweden on a national level. They calculated the risk of cerebral hemorrhage in cancer patients based on Sweden's national population. The results indicated that the incidence of cerebral hemorrhage within 6 months, 6 months to 1 year, and 1 year to 5 years was 2.2%, 1.4%, and 1.3%, respectively. This indicates that the risk of cerebral hemorrhage in cancer patients is significantly higher than that in the healthy population. Similarly, the results indicate that the risk of cerebral hemorrhage increases in patients with liver cancer. In particular, cerebral hemorrhage develops within about 6 months after the diagnosis of liver cancer, as confirmed in these patients.

There are some characteristic features in liver cancer patients who developed cerebral hemorrhage. Zhang et al. [4] retrospectively reviewed the clinical data of 69 cancer patients who had developed the complication of stroke from January 1999 to December 2004, including 13 cancer patients who had developed the complication of cerebral hemorrhage. We found that the most common site of hemorrhage was in the lobes of the brain (8 patients, 61.5%), and the prognosis of most patients was poor. In the present study, no particular signs were observed in the hemorrhage lesion site when we performed brain CT of these patients. However, we found that 1 or more tumor markers were elevated in the plasma of all patients. Most of these patients had abnormal levels of coagulation and liver function. These were the significant clinical features of these patients.

Pathogenesis of hepatic cancer with cerebral hemorrhage

The pathogenesis of cerebral hemorrhage is very complicated, and we still do not know whether the pathogenesis of liver cancer and cerebral hemorrhage is related to cancer or not. This is a pertinent issue that needs to be resolved. Navi et al.4[7] investigated 208 cancer patients with intracranial hemorrhage in Memorial Sloan-Kettering cancer center from 2000 to 2007 analyzing the causes and prognosis of these patients. The results indicated that 141 patients had non-hematological system cancer, which was complicated with cerebral hemorrhage. Among them, 98 (69.50%) patients had developed bleeding due to brain metastasis; 55 (39.01%) had coagulation dysfunctions, and 33 (23.40%) had developed bleeding within the tumor along with coagulation dysfunctions. This indicates that intracranial metastasis and coagulation dysfunctions are the common characteristics of cancer patients with cerebral hemorrhage. Their study also proved that there were other uncommon causes of cancer with cerebral hemorrhage. This included 9 patients (6.38%) with hypertensive cerebral hemorrhage, 6 (4.26%) with traumatic cerebral hemorrhage, 4 (2.84%) with cerebral hemorrhage after cerebral infarction, and 3 (2.13%) with cerebral artery aneurysms. Cerebral hemorrhage was caused by cerebral venous thrombosis in only 1 patient (0.71%). These results indicate the pathogenesis of cancer with cerebral hemorrhage is indeed a complicated issue. In the present study, there were only 2 patients with hypertension (patients #4 and #5) and 5 did not have any risk of developing stroke (patients #2, #3, #6, #7, and #8). However, blood

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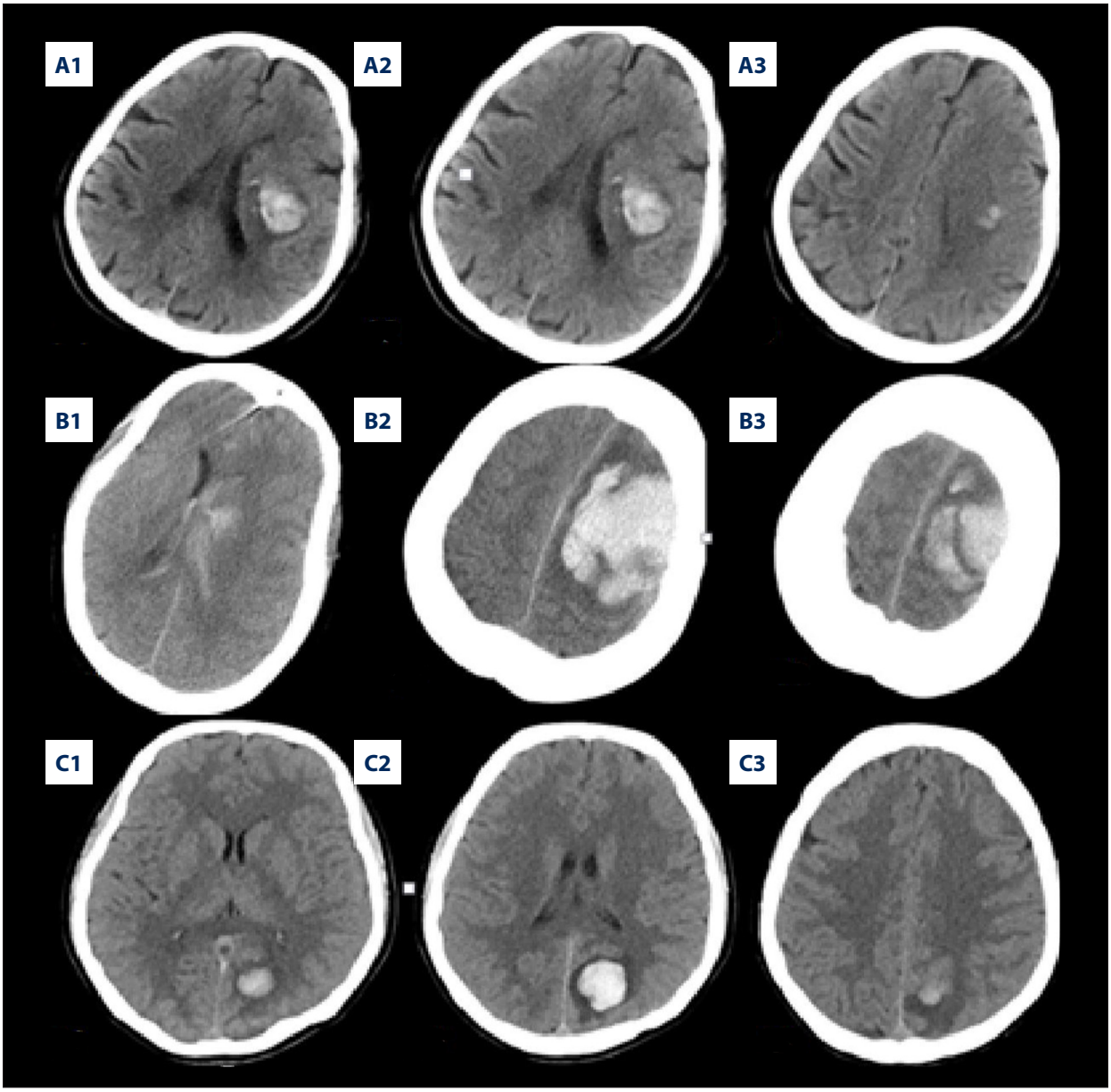

Figure 1. CT images showing cerebral hemorrhage. (**A1–A3**) Patient #5 with traditional risk factors of cerebral hemorrhage; the patient was hospitalized as soon as cerebral hemorrhage was detected. Subsequently, liver cancer was detected in this patient at 1 day after admission. CT images showed that a cerebral hemorrhage had developed at the left basal ganglion. (**B1–B3**) Patient #7 did not have any traditional risk factors of cerebral hemorrhage; however, 12 months after the diagnosis of liver cancer, the patient developed cerebral hemorrhage. A CT scan showed that a cerebral hemorrhage had developed in the left parietal lobe. (**C1–C3**) Patient #8 also did not have any traditional risk factors for cerebral hemorrhage. The patient was hospitalized due to cerebral hemorrhage and was diagnosed with liver cancer 6 days after admission. A CT scan showed that a cerebral hemorrhage occurred at the left occipital lobe.

biochemistry tests showed that 8 patients had coagulation dysfunctions, indicating that coagulation dysfunctions might be the main cause of liver cancer with cerebral hemorrhage. Previous research proved that in patients with liver cancer, coagulation dysfunctions are mainly caused by a reduction in the number of platelets and clotting factors, activation of the fibrinolytic system, and extensive DIC [13–15]. Moreover, some common chemotherapy drugs, such as bleomycin, mitomycin C, and cytarabine, might aggravate coagulation dysfunctions [26–28].

In the present study, we hospitalized 5 patients who developed cerebral hemorrhage. Interestingly, the traditional risk

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Table 2. Clinical data of cerebral hemorrhage in 9 patients.

Number	Gender	Age (year)	Bleeding time (day)	Traditional risk factors	Main clinical presentations	Site of cerebral hemorrhage on brain CT	NIHSS or GCS (scale)	mRS (scale)
1	Male	70	–1	A history of Cerebral infarction	Fever, disturbance of consciousness	Left parietal lobe	GCS 8	5
2	Male	48	335	N	Sudden limb weakness, loss of speech, vomit	Left temporoparietal lobe	GCS 5	4
3	Female	51	–15	N	dizziness	Basal ganglion	NIHSS 1	0
4	Male	65	20	High cholesterol, hypertension, smoking and drinking	Sudden seizure, dizziness, limb weakness	Right temporal lobe	NIHSS 2	0
5	Male	57	–1	Hypertension, cerebral hemorrhage	Unclear consciousness, vomit	Left thalamus	GCS 7	3
6	Male	56	395	N	Sudden coma	Pons	GCS 6	6
7	Female	70	365	N	Sudden fall, disturbance of consciousness and no response	Left parietal lobe	GCS 8	3
8	Female	73	–6 d	N	sudden headache, vomit	Left occipital lobe	NIHSS 1	0
9	Male	65	–11 d	Smoking drinking	Left limb weakness	Right basal ganglion	NIHSS 4	1

NB – time of hemorrhage was duration between cerebral hemorrhage and diagnosis of liver cancer, the day of diagnosis of liver cancer is recorded as zero, positive days means that cerebral hemorrhage occurred after the diagnosis of liver cancer; Negative days means that cerebral hemorrhage occurred before the diagnosis of liver cancer; N – no traditional risk factors.

factors for cerebral hemorrhage were never found in 2 out of 5 patients. Furthermore, liver cancer was diagnosed during their course of treatment. Nevertheless, coagulation functions were abnormal, and the level of tumor markers such as AFP was elevated in the plasma. Thus, we found further evidence to ascertain the relevant factors causing cerebral hemorrhage. Although there was no imaging to prove that brain metastasis from liver cancer does not occur prior to cerebral hemorrhage, we could not exclude the possibility of bleeding caused by brain metastasis of liver cancer. Previous research proved that when brain CT and MRI of patients showed various signs, such as strengthening effect around a hematoma, various densities within a hematoma, delayed progression of hematoma, reduction or lack of hemosiderin, and continuous swelling surrounding a hematoma, we deduced that the patient had developed intracranial tumor hemorrhage [29–31].

This was a retrospective study; therefore, we recruited a limited number of patients. The clinical data of hospitalized patients only met the criteria of clinical diagnosis. All these confounding factors are limitations in our study investigating the clinical features and pathogenesis of liver cancer patients who suffer cerebral hemorrhage as a complication. Therefore, a prospective study must be conducted in a multicenter community setting of this population. With this novel approach, we can comprehensively decipher the pathogenesis of liver cancer complicated by cerebral hemorrhage. Thus, we can devise various therapeutic treatments that are appropriate for managing this condition.

Conclusions

This study describes theunique pathophysiology and clinical features of patients who have liver cancer complicated with cerebral hemorrhage. Coagulopathy cause most cerebral hemorrhage in patients with liver cancer, whereas hypertension and other causes typical in the general community are rare. The site of cerebral hemorrhage is often detected in the lobes of the brain and the prognosis is generally poor.

Conflict of interest

None.

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