

Clinical Characteristics of Spinal Involvement in Hepatocellular Carcinoma

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Abstract-

Purpose: To analyze the clinical characteristics of hepatocellular carcinoma (HCC) with spinal metastasis.

Methods: During a period of 14 years, 42 HCC patients with cranial and/or spinal metastasis were identified. Among them, 12 had spinal involvement and thus were included for study. The clinical, laboratory and neuroimaging data of these 12 cases were analyzed.

Results: The 12 cases were all male, aged 36-65 years. The time interval from the diagnosis of HCC to the finding of spinal involvement was 0-38 months. Among these 12 cases, four had the features of spinal involvement in the initial presentation of their HCC. Low back pain was the most common symptom followed by weakness and numbness in the lower limbs. A serum biochemical study did not show unique findings. All 12 cases died within nine months after the diagnosis of the HCC spinal involvement.

Conclusions: 28.6% (12/42) of the HCC patients with nervous system metastasis had spinal involvement and the exact incidence rate can be increased by more extensive neuroimaging studies. Viral hepatitis and liver cirrhosis are common preceding events in patients with HCC with spinal involvement. T- and L-spine are the most commonly involved segments and back pain is the most common complaint in patients with HCC with spinal metastasis. The prognosis in this group of patients is grave and most of the patients died soon after the development the HCC's spinal involvement. No specific biomarker can predict the development of spinal involvement in HCC patients and diagnostic consideration can only be emphasized, especially in HCC hyperendemic areas such as Taiwan.

Key Words: Hepatocellular carcinoma, Nervous system metastasis, Spinal metastasis

Acta Neurol Taiwan 2009;18:255-261

INTRODUCTION

Taiwan is one of the important hyperendemic areas

for hepatocellular carcinoma (HCC)⁽¹⁻³⁾, which is an important and leading lethal malignancy, especially in males^(2,4). Local, extrahepatic metastasis of HCC are

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Received February 5, 2009. Revised March 2, 2009.

Accepted June 12, 2009.

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common^(5,6) and the lungs, adrenal gland and bone marrow are frequent sites for these distant metastasis⁽⁵⁻¹⁰⁾. The nervous system is still not a common site for HCC metastasis⁽⁵⁻¹⁰⁾. With the improvements in diagnostic tools and treatment modalities, the survival times of HCC patients have been prolonged⁽¹¹⁾. Therefore, nervous system involvement in HCC patients is expected to increase but it is still underestimated because of the rapid and lethal clinical course, especially after the development of hepatic encephalopathy^(1,2,12). Where the nervous system is involved, spinal involvement is still uncommon^(2,13,14-17). We analyzed the clinical features and therapeutic outcomes of 12 HCC patients with spinal involvement in order to delineate the clinical characteristics of spinal metastasis in cases of HCC.

MATERIALS AND METHODS

During a period of 14 years (January 1993 to December 2006), 42 HCC patients with cranial and/or spinal involvement were identified at Chang Gung Memorial Hospital (CGMH)-Kaohsiung. Twelve of the 42 patients had spinal involvement and thus were included for study.

The 12 HCC cases with spinal involvement had spinal computed tomography (CT) and/or magnetic resonance imaging (MRI) to confirm the existence of spinal involvement. The diagnosis of HCC spinal metastasis was further confirmed by the following criteria: (1) a positive liver biopsy characterized by the similarity of tumor cells to hepatic cord cells^(18,19), (2) a positive spinal

Table. The basic clinical data of the 12 hepatocellular carcinoma patients

Patient no.	Sex	Age at spinal metastasis (years)	Survival after spinal metastasis (months)	Other metastatic areas	Clinical presentation
1	M	53	2		Bilateral leg weakness and numbness, low back pain, urine retention
2	M	51	7		Right leg weakness and numbness, low back pain
3	M	58	9	Lung, bone	Left arm weakness and numbness, neck pain with radiation to left arm
4	M	54	6	Bone	Left leg numbness, urine retention, constipation
5	M	52	3	Skull, bone	Bilateral leg weakness and numbness, urine retention, constipation
6	M	44	1	Lung, skull, bone	Bulbar palsy
7	M	36	2	Lung, bone	Bilateral leg weakness and numbness, low back pain, urine retention, constipation
8	M	65	7		Left leg numbness, low back pain
9	M	65	2		Left leg weakness, low back pain
10	M	59	5	Bone	Bilateral leg weakness and numbness, low back pain
11	M	56	4	Cerebellum, Lung, bone	Low back pain
12	M	48	7	Occipital	Right leg numbness, low back pain

M: male; C: cervical spine; T: thoracic spine; L: lumbar spine; DM: diabetes mellitus; NA: not available; α -FP: alpha-fetoprotein (normal range: <15); AST: aspartate aminotransferase (normal range: 0-37); ALT: alanine aminotransferase (normal range: 0-40);

biopsy with histopathological characteristics of HCC. Patients without tissue proof were confirmed by the radiographic criteria of HCC^(2,20), which includes a mass > 2 cm in diameter in a cirrhotic liver in two imaging modalities, and contrast enhancement on CT, MRI, or angiography. A mass lesion within a cirrhotic liver in the presence of a serum alpha-fetoprotein (α -FP) level > 400 ng/ml is also diagnostic. In this study the presenting symptoms, age at HCC diagnosis, time interval from the diagnosis of HCC to the finding of HCC spinal involvement, size of the primary tumor, liver biochemistry, number and location of spinal involvement, preceding medical problems, clinical presentations of spinal involvement, and duration of survival after HCC spinal involvement were all recorded for analysis.

RESULTS

The clinical and laboratory data of the 12 cases are listed in Table. Examples of HCC spinal involvement are shown in Fig. All 12 cases were male, with age of HCC diagnosis ranging from 36 to 65 years (mean = 51.8 years). The interval from the diagnosis of HCC to the findings of spinal involvement was 0 to 38 months (mean = 10.12 months). Four cases (patients 3, 4, 9, 12) were found to have spinal involvement before the diagnosis of HCC. Spinal metastasis was confirmed by spinal biopsies in six cases (patients 2, 3, 4, and 6, 7, 8), by radiographic criteria in five cases (patients 1, 5, 10, 11, 12), and by mass lesions within a cirrhotic liver in the presence of high serum α -FP levels in one case

Table. The basic clinical data of the 12 hepatocellular carcinoma patients

Underlying medical condition	α -FP (ng/ml)	AST (U/L)	ALT (U/L)	Alb (g/dl)	T-bil (mg/dl)	INR	PLT ($10^3/cm^3$)	ALK-P (U/L)	Child-Pugh score	Image of cranial and spinal involvement
Hepatitis B, liver cirrhosis	9334	46	44	4	0.8	1.15	15.6	181	6	T6, L5
Hepatitis B, liver cirrhosis	442	269	347	4.5	1.2	1.14	11.2	201	5	L5
Liver cirrhosis	60500	98	84	3.9	0.8	NA	16.7	NA	NA	C7
Hepatitis B, liver cirrhosis	219	60	42	4.1	0.4	1.04	30.7	NA	5	T3~T7
Hepatitis B and C, DM, liver cirrhosis	31.4	146	93	4.4	1.4	0.93	15.3	130	5	T9, L1, L4~L5
Hepatitis B, liver cirrhosis	3.8	101	149	NA	0.9	NA	NA	NA	NA	C1 with skull base extension
Liver cirrhosis	19860	384	124	2.9	1.9	1.14	10	185	6	T3
Hepatitis C, liver cirrhosis	291.43	56	79	3.1	1.1	NA	5.9	66	NA	T7, T8
Liver cirrhosis	1665	207	62	NA	0.8	NA	NA	NA	NA	T11
Hepatitis C, liver cirrhosis	291.43	52	23	3.1	0.9	1.14	25.9	90	6	L1
Hepatitis B, liver cirrhosis	464584	64	24	3.5	1.3	1.15	8.9	149.33	6	L2
Hepatitis B and C, DM, liver cirrhosis	3.41	47	100	3.3	1.7	1.12	33.5	72.86	6	C2, right cerebellum

Alb: albumin (normal range: 3.0-5.0); T-bil: total bilirubin (normal range: 0.2-1.4); PLT: platelet (normal range: 150-400); ALK-P: alkaline phosphatase (normal range: 28-94).

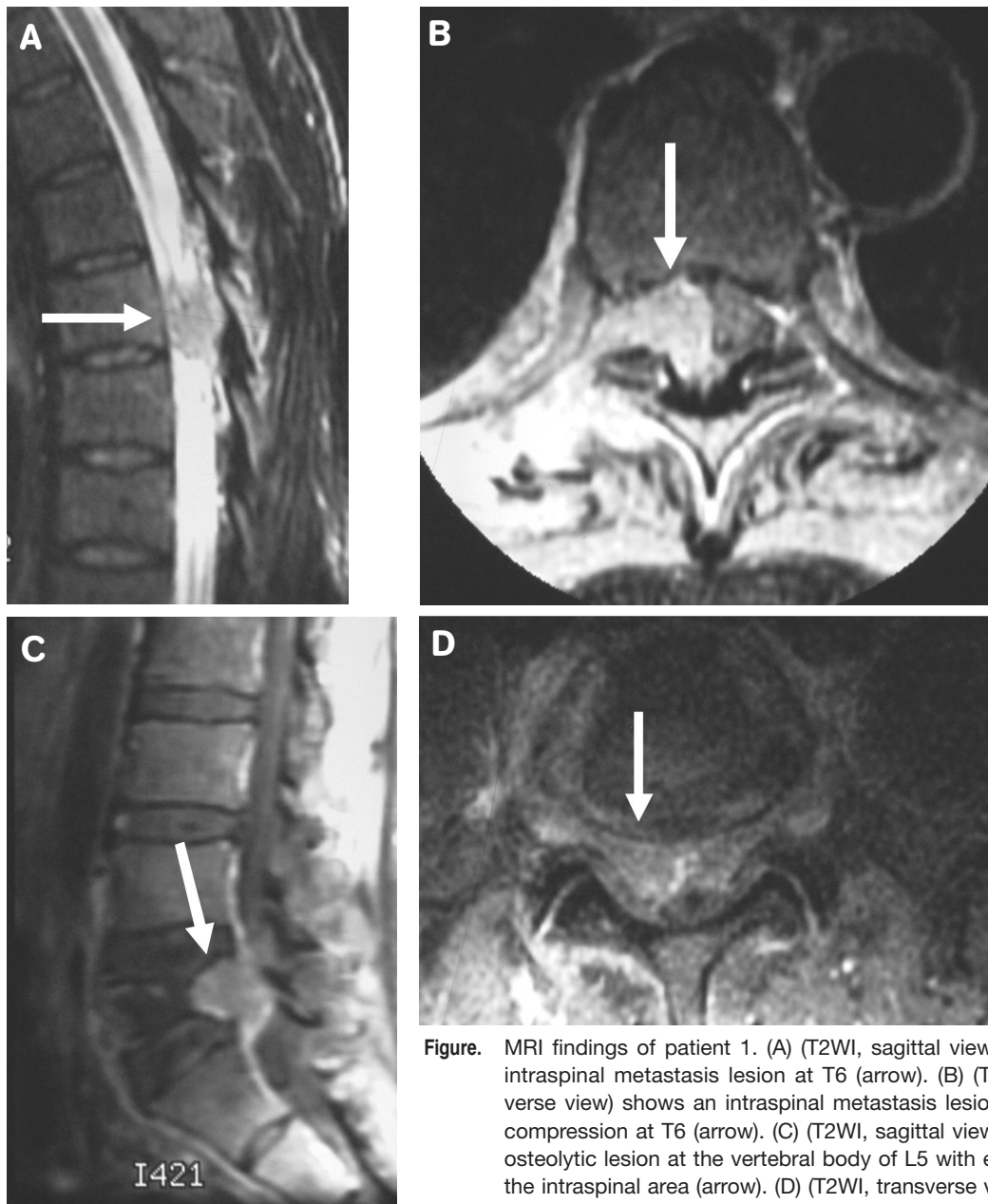


Figure. MRI findings of patient 1. (A) (T2WI, sagittal view) shows an intraspinal metastasis lesion at T6 (arrow). (B) (T2WI, transverse view) shows an intraspinal metastasis lesion with cord compression at T6 (arrow). (C) (T2WI, sagittal view) shows an osteolytic lesion at the vertebral body of L5 with extension to the intraspinal area (arrow). (D) (T2WI, transverse view) shows spinal canal invasion at L5 with vertebral body destruction (arrow).

(patient 9). Three (patients 1, 2, 10) out of the 12 cases had a positive family history of HCC.

Among these 12 cases, underlying hepatitis was noted in nine cases, with hepatitis B in five cases (patients 1, 2, 4, 6, 11), hepatitis C in two cases (patients 8, 10) and both hepatitis B and C in two cases (patients

5, 12). All 12 cases had liver cirrhosis. As shown in Table, serum biochemical studies showed elevated aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels in all 12 cases, elevated α -FP in nine cases (patients 1-5, 7, 8, 10, 11), elevated total bilirubin levels in two cases (patients 7, 12), elevated alkaline-

phosphatase levels in eight cases (patients 1, 2, 5, 7, 8, 10, 11, 12), a decreased albumin level in one case (patient 7), and decreased platelet counts in four cases (patients 2, 7, 8, 11). None of the tested patients had a prolonged international normalization ratio of prothrombin time (PT INR).

In the imaging findings, all 12 cases had an HCC mass in the right hepatic lobe, with a tumor size ranging from 1.6 cm to 11 cm (mean = 7.0 cm). Of the locations of spinal involvement, the thoracic (T) spine was noted in six cases (patients 1, 4, 5, 7, 8, 9), lumbar (L) spine in six (patients 1, 2, 5, 10, 11, 12), and cervical (C) spine in three (patients 3, 6, 11). Three patients had multiple spinal segment involvement with patients 1 and 5 at both T- and L- spines, and patient 11 at both C- and L- spines. Four cases had both cranial and spinal involvement. Of these four cases, two (patients 5, 6) had a concomitant skull involvement at the time of the finding of spinal involvement. The remaining two cases (patients 11, 12) had cranial involvement after the finding of spinal metastasis. Of these two cases, one (patient 11) had a cerebellar involvement and one (patient 12) had an occipital lobe involvement.

All 12 cases had a full consciousness (Glasgow Coma Scale (GCS) score = 15) at the time of finding HCC spinal involvement, while the GCS scores of the other 30 cases with known HCC cranial metastasis were 8 to 15 (mean = 13.1). This difference in GCS scores between these two groups of patients was statistically significant ($p = 0.027$, t -test). As shown in Table, the main neurological manifestations in these 12 cases were low back pain (LBP) (75.0%, 9/12), limb weakness (58.3%, 7/12), numbness (58.3%, 7/12), urination problems (33.3%, 4/12) and defecation problems (25%, 3/12). The presenting cranial features in the four cases with cranial involvement were subsequent consciousness disturbance (patient 12), seizures (patient 11), bulbar palsy (patient 6), and one without clinical symptoms (patient 5). Child-Pugh scores were assessed in eight cases (patients 1, 2, 4, 5, 7, 10, 11, 12), with scores of 5-6.

For spinal involvement, one case (patient 2) received a spinal operation, five cases (patients 1, 4, 5, 6, 10)

received radiotherapy and three cases (patients 3, 7, 12) received both spinal operations and radiotherapy. Three cases (patients 8, 9, 11) did not receive any treatment of their spinal involvement. As compared with the laboratory data of the cases with only spinal HCC metastasis, the four cases with cranial involvement had similar laboratory data findings. However, when considering the size of the primary HCC tumor, the tumor sizes of the cases with cranial involvement were 5.3 cm to 11 cm (mean = 9.10 cm) as compared to 2.4 cm to 6 cm (mean = 3.75 cm) in the other eight cases with spinal involvement only. This tumor size difference between these two groups of patients was of statistical significance ($p = 0.044$, t -test).

DISCUSSION

Our previous study⁽²⁾ showed that nervous system involvement was detected in 0.28%, an underestimated incidence, of the total number of HCC patients and only 0.04% had the concomitant signs and symptoms on presentation. In this study, only 28.6% (12/42) of the HCC patients with nervous system involvement were found to have spinal involvement. Although neuroimaging studies are not regularly arranged in the management of HCC patients, the relatively lower incidence of spinal involvement than cranial involvement in HCC metastasis can be explained partially by the lower initial consciousness level and possible subsequent neglect of the spinal symptoms of the later group of patients. However, it should be emphasized that nervous system involvement (spinal and cranial involvement) is usually underestimated in HCC patients, especially when late stage HCC patients have obvious clinical evidence of hepatic encephalopathy^(2,21). The exact incidence of spinal involvement in HCC metastasis can be delineated by further large-scale and more extensive neuroimaging studies of HCC patients.

In this study, the most commonly involved spinal segments were the T- and L-spines. This finding is consistent with that of reported metastatic spinal lesions including those with HCC spinal involvement^(9,22,23). It is difficult, especially in the early stages, to trace exactly how metastatic HCC is spread to the T- and L- spinal

segments, but it may be through pulmonary circulation or the vertebral venous plexus⁽²³⁻²⁵⁾. This predilection of T- and L- spine involvement in HCC extrahepatic metastasis may explain the reason why back pain, especially LBP, and dysfunction of the lower limbs were the main neurologic presentations in this group of patients. The finding is also consistent with that of other reports^(1,8,9,22,23).

This study showed a high incidence of viral hepatitis (75%, 9/12) and liver cirrhosis (100%, 12/12) among the 12 HCC patients with spinal involvement. These high incidences of liver diseases may be due to the high prevalence of viral hepatitis and liver cirrhosis in HCC patients in Taiwan⁽²⁶⁾. In addition, all 12 included patients were male. The high incidence of male gender in HCC, including those with nervous system involvement, has been noted before^(1,2,21) and this predilection can be explained by the male predominance of hepatitis virus infection in Taiwan^(2,27).

As shown in Table, all 12 patients had elevated serum AST and ALT levels. The serum biochemical data were not unique and they are similar to those of other HCC patients with or without nervous system involvement^(2,21). Clinically, so far, no commonly used biomarkers are capable of predicting nervous system involvement^(2,9-17,21). Four of the 12 patients had spinal involvement as the presentation of HCC. Therefore, the diagnosis of HCC nervous system metastasis including spinal involvement can only be made by thorough hepatic and spinal imaging studies, serum α -FP detection and histopathologic confirmation^(2,12,21,28). This consideration should be emphasized especially in hyperendemic areas of HCC such as Taiwan.

This study revealed that in patients with HCC spinal metastasis, a larger initial primary HCC size may increase the chance of cranial involvement, but the value of this conclusion is limited by the small patient number. Even though the primary HCC tumor size could be used to predict the prognosis⁽²³⁾, further large-scale studies are needed to better delineate the relationship of the involved areas. A study of clinicopathology examination of HCC conducted by Lai et al. has shown that 58.5% of HCC located at the right lobe and 34.2% located bilaterally. Our study result revealed that all twelve cases had

their HCC located at the right lobe. This predilection of HCC with spinal involvement also needs further large-scale study for delineation. Despite the fact that eight of the 12 patients had a Child-Pugh score assessment at the Child A classification, which is presumed to have virtually no risk for mortality from liver-related causes during the subsequent year⁽²⁹⁾, all 12 patients died within nine months after the diagnosis of HCC spinal involvement. This grave therapeutic result of HCC with spinal involvement is consistent with the findings of previous reports of HCC with nervous system involvement^(2,12,21), in which all the involved patients died within one year.

In conclusion, 28.6% of the HCC patients with nervous system metastasis had spinal involvement and the exact incidence rate can be increased by more extensive neuroimaging studies. Viral hepatitis and liver cirrhosis are common preceding events in patients with HCC spinal involvement. The T- and L-spines are the most commonly involved segments and LBP is the most common complaint of patients with HCC spinal metastasis. Although modern technologies for the diagnosis and treatment of HCC have improved greatly, the prognosis of this group of HCC patients with spinal involvement is still grave and most of the patients died soon after the development of spinal metastasis. No specific biomarker can predict the development of spinal involvement in HCC patients and diagnostic consideration can only be emphasized, especially in HCC hyperendemic areas such as Taiwan.

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