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PORTAL HYPERTENSION AND VARICEAL BLEEDING

Characteristics of hepatocellular carcinoma presenting with variceal bleeding

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Abstract Patients with hepatocellular carcinoma may present with variceal bleeding as the initial symptoms. The aims of this study is to investigate the characteristics of such patients. A total of 1046 hepatocellular carcinoma cases were retrospectively retrieved from our computer records between 1980 and 1993. The medical records and image studies were reviewed. The status of each patient was assessed at the time of presentation. A total of 14 (about 1%) patients with hepatocellular carcinoma presented with variceal bleeding. Five (36%) did not have past history of liver disease. The tumour size ranged from 2.5 to 11.3 cm. Compared with hepatocellular carcinoma patients not presenting with variceal bleeding, these patients had a higher percentage of portal vein thrombosis (57.1 *vs* 19.4%). In two patients, the hepatic tumours were missed in the initial abdominal sonography. The average survival time was 71 days. Seven patients died within 2 months mainly due to variceal bleeding (41.6%). Variceal bleeding might be a clue to the presence of hepatocellular carcinoma with portal vein thrombosis even in patients without a previous history of liver disease. The tumours in such patients might be the infiltrative type, and thus the portal vein should be carefully worked-up. Overall, these patients have an extremely poor prognosis. In the management of patients with variceal bleeding, the possibility of hepatocellular carcinoma with portal vein thrombosis should not be overlooked, especially in areas where this cancer is prevalent.

Key words: bleeding, gastric varices, hepatocellular carcinoma, oesophageal varices, portal vein thrombosis, presentation, prognosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the commonest malignancies in the world, especially in sub-Saharan Africa and South-East Asia.[1,2] Since 1984, it has been the leading cause of cancer deaths in Taiwan. Between 6000 and 8000 people die of this cancer every year in Taiwan.[3] The prognosis of symptomatic HCC is very poor, with a mean survival of only a few months after the onset of symptoms.[4] Common symptoms in advanced HCC include general malaise, anorexia, nausea, vomiting, abdominal fullness, palpable mass, bodyweight loss, jaundice, oedema and abdominal pain.[4] Traditionally, the clinical presentations of HCC have been classified as frank, cirrhotic, occult, febrile, acute abdomen, metastatic and icteric types.[5] We observed that bleeding from oesophageal varices (EV) or gastric varices might also be the first presenting symptom in HCC patients. Such presentations of HCC have not been emphasized before. In this paper, we detail the characteristics of HCC presenting with variceal bleeding, and the importance of this presentation is stressed.

METHODS

HCC presenting with variceal bleeding was defined as follows: HCC which were diagnosed within several days of the first variceal bleeding episode. HCC diagnosed before the first variceal bleeding episode or diagnosed long after (>1 month) the first variceal bleeding episode were excluded. Bleeding from varices was defined by

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the endoscopic observation of actively bleeding varices or by the presence of prominent varices in a bleeding patient when no other source of haemorrhage was evident.[6] The diagnosis of HCC was made by pathological proof or by the elevated serum α-fetoprotein (AFP) (> 400 ng/mL) level and typical sonographic or computed tomographic findings. A total of 1046 HCC cases which occurred between 1980 and 1993 in the National Taiwan University Hospital were retrospectively retrieved from our computer records. The medical records and image studies were reviewed. The status of each patient was assessed at the time of presentation.

RESULTS

A total of 14 HCC cases presented with variceal bleeding, including 13 males and one female with a mean age of 57 years (range 34–74) (Table 1). The incidence of HCC presenting with variceal bleeding was about 1% in this series. Among these 14 HCC patients, five (35.7%) patients had no previous history of liver disease. The remaining nine (64.3%) patients had known liver disease for 1 to 10 years. However, none of them had regular follow up for their liver diseases. All of the 14 patients had liver cirrhosis when assessed in their first bleeding episode. The liver status according to Pugh's modification of Child's classification was Child's A in five (35.7%) cases, Child's B in five (35.7%) cases, and Child's C in four (28.6%) cases. On presentation, nine (64.3%) patients had no other symptoms except the bleeding. The other five patients had abdominal fullness, right upper quadrant pain or bodyweight loss. Only one patient presented with shock. The other 13 patients had their systolic blood pressure above 100 mmHg. Only two patients had a haemoglobin level above 10 g/dL, the remaining 12 patients had moderate to severe anaemia (haemoglobin levels from 3.5 g/dL to 9.7 g/dL).

Sonographically, the tumours in eight (57.1%) patients appeared as well-defined nodules in the liver (nodular type). In four (28.6%) patients, the tumours appeared as an ill-defined mass with unclear margins (infiltrative type). In the remaining two (14.3%) patients, the tumour appeared as a massive tumour with or without small satellite nodules (massive type).[7] The tumour sizes varied from 2.5 to 11.3 cm. The tumour size was less than 3 cm in two cases, between 3 and 5 cm in four cases, more than 5 cm in three cases. The tumour size was difficult to measure in three cases because of the ill-defined tumour area (Table 2). The initial sonography did not detect the hepatic tumours in two patients. These two tumours were first detected by abdominal computed tomography, which revealed ill-defined hypodense hepatic tumours. Eight patients (57.1%) had portal vein thrombosis (PVT), mainly involving the main portal vein. On the contrary, PVT was detected in 201 (19.4%) of the remaining 1032 HCC. The difference was statistically significant ($P < 0.05$, Fisher's exact test). Two of the 14 patients received biopsy for their hepatic tumours. Both showed Edmondson grade II trabecular HCC. Two (14.1%) patients received transcatheter arterial embolization (TAE) for their HCC, while the others received only supportive treatment for the HCC (Table 3).

For the control of the variceal bleeding, nine (64.3%) patients received endoscopic injection sclerotherapy or endoscopic variceal ligation (Table 3). The remaining five patients received pitressin infusion. However, the bleeding could not be stopped in five of the 14 patients, and they died of massive variceal bleeding. In another two patients, the massive bleeding *per se* did not cause death, but it precipitated hepatic encephalopathy, leading to the patients' death.

With the exception of the two patients who were lost

Table 1 Basic and clinical data in the variceal bleeding type hepatocellular carcinoma patients

Patient no.	Sex	Age	Previous history of liver disease	Symptoms besides bleeding	Child's classification	BP (mm Hg)	Hb (g/dL)	HBsAg	anti-HCV	AFP (ng/mL)
1	M	39	CLD (3 years)	RUQ pain	A	110/70	8.5	+	ND	> 3200
2	M	57	CLD (1 year)	Nil	C	120/70	9.7	+	ND	11525
3	M	34	CLD (3 months)	General malaise	C	140/70	7.2	+	–	4170
4	M	74	LC (1 year)	Nil	B	168/100	6.8	+	ND	2975
5	M	61	Not known	Bodyweight loss	B	100/60	11.0	–	ND	> 35000
6	M	44	Not known	Nil	A	110/60	8.8	+	–	> 35000
7	M	53	CLD (8 years)	Nil	A	120/74	3.5	+	ND	> 3200
8	M	72	CLD (8 years)	Nil	C	100/70	9.5	+	ND	> 70000
9	M	64	LC (4 years)	Nil	A	112/68	7.6	–	ND	2808
10	M	70	Not known	Abdominal fullness	B	140/90	13.0	+	ND	< 20
11	M	57	CLD (10 years)	Nil	B	84/50	8.2	+	+	> 35000
12	M	53	Not known	Abdominal fullness	C	130/70	7.4	+	–	2035
13	M	63	Not known	Nil	B	108/70	9.0	+	ND	24935
14	F	58	LC (3 years)	Nil	A	122/80	6.8	–	+	37480

CLD, chronic liver disease; LC, liver cirrhosis; RUQ, right upper quadrant; AFP, alpha-fetoprotein; ND, not done; BP, blood pressure; Hb, haemoglobin; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus.

Table 2 Abdominal sonogoraphic findings in the variceal bleeding type hepatocellular carcinoma

Patient no.	Characteristics	Tumour no.	Tumour size (cm)	Location	PVT
1	Hypoechoic, well-defined, clear margin	Multiple	ND	Bilat	?
2	Hyperechoic, well-defined, clear margin	1	4.0	Rt	–
3*	Hypoechoic, ill-defined, unclear margin	Multiple	7.3	Rt	Main and bilat
4	Mixed echogenic, well-defined, clear margin	1	3.2	Rt	Rt
5#	Hypoechoic, ill-defined, unclear margin	?	?	Rt	Main and bilat
6	Hypoechoic, well-defined, irregular margin	1	4.9	Lt	Main and bilat
7#	Hypoechoic, ill-defined, margin ?	Multiple	?	Bilat	Main and ? bilat
8#	Ill-defined, unclear margin	?	?	Rt	Main and bilat
9	Hypoechoic, well-defined	Multiple	ND	Bilat	Rt
10	Hyperechoic, well-defined	2	2.5	Rt	–
	hypoechoic, well-defined		3.5		
11	Hypoechoic, well-defined, clear margin	1	2.5	Rt	–
12	Hyperechoic, ill-defined, irregular margin with multiple small hypoechoic tumours	Multiple	11.3	Bilat	Main
13*	Slightly hypoechoic, well-defined, irregular margin	1	3.2	Rt	–
14	Hyperechoic, well-defined	1	6.5	Rt	–

*No tumour was found in previous sonography several days ago; #the tumour area was difficult to define; PVT, portal vein thrombosis; Rt, right; Lt, left; Bilat, bilateral; ND, not done; ?, not clear.

Table 3 Treatments and outcomes in the variceal bleeding type hepatocellular carcinoma patients

Patient no.	Treatment for varices	Treatment for tumour	Follow-up duration	Outcome	Cause of death
1	Pitressin	Supportive	27 days	Lost follow up	
2	EVL	Supportive	238 days	Death	Tumour rupture
3	EVL	Supportive	98 days	Death	Unknown
4	EIS	Supportive	22 days	Death	Variceal bleeding
5	EIS	Supportive	34 days	Death	Variceal bleeding
6	EVL	Supportive	157 days	Death	Liver failure
7	Pitressin	Supportive	24 days	Death	Variceal bleeding
8	EVL	Supportive	11 days	Death	Variceal bleeding
9	Pitressin	Supportive	40 days	Death	Variceal bleeding
10	Pitressin	TAE	156 days	Lost follow up	
11	EIS	Supportive	63 days	Death	Liver failure
12	Pitressin	Supportive	33 days	Death	Liver failure
13	EIS	TAE	111 days	Death	Liver failure
14	EIS	Supportive	23 days	Death	Sepsis

EIS, endoscopic injection sclerotherapy; EVL, endoscopic variceal ligation; TAE, transcatheter arterial embolization.

to follow up, all the remaining 12 cases died. The average survival time was 71 days (range 11 to 238 days) after the bleeding episode. Seven (58.3%) patients died within 2 months. The main cause of death was variceal bleeding (41.6%) followed by liver failure (33.3%, Table 3).

DISCUSSION

Variceal bleeding is universally recognized as a serious, often fatal complication of portal hypertension.[8] It is well-known that EV bleeding is usually a terminal event in unresectable HCC.[4] However, it has often been overlooked that variceal bleeding might also be the initial presenting symptom in HCC. In our daily practices, we observed that unexplained decompensation in liver function might foretell the presence of HCC (Chen *et al.* unpubl. obs., 1997). Likewise, although the most common cause of variceal bleeding is due to cirrhosis-associated portal hypertension, variceal bleeding might also imply portal hypertension resulting from PVT of HCC. This point should be emphasized because it is possible that some HCC were overlooked because the variceal bleeding was attributed only to liver cirrhosis *per se*.

About 1% of our overall HCC patients presented with variceal bleeding. This was much lower than the

number presenting in Japan as a whole (5.4%).[9] Our data may be an underestimate, as some patients with massive haematemesis died before they could receive the endoscopic examination to confirm the bleeding source or any diagnostic modality to detect their HCC. These patients were thus excluded from the present study.

In this series, 57% of our HCC patients presenting with variceal bleeding had PVT in the initial presentation. The percentage of PVT was higher (19.4%) than that detected in our HCC patients not presenting with variceal bleeding. This means that although liver cirrhosis with portal hypertension was an important factor leading to variceal bleeding, PVT also played an important role in the pathogenesis of HCC presenting with variceal bleeding. Yeo *et al.*[10] found that PVT was detected in 76% of the variceal bleeding HCC patients, compared with only 45% of the non-variceal bleeders. The higher percentage of PVT in their series may be due to the different timing for detecting PVT between their series and our present study. In their series, HCC was diagnosed first and then the portal vein status was re-assessed during the later bleeding episode. Portal vein thrombosis may aggravate the cirrhosis-associated portal hypertension, or it may lead to portal hypertension in patients without liver cirrhosis,[10–12] thus leading to the variceal bleeding. However, about two-thirds of the 14 HCC patients were B or C according to Pugh's modification of Child's classification; the more severe underlying liver cirrhosis in these 14 HCC patients may be a confounding factor for the present analysis.

It is very important to note that 35.7% of our patients did not have a previous history of liver disease and the remaining 64.3% of patients did not have regular follow up for their known liver diseases. Besides, 64% of our patients had no other symptoms except the bleeding. It was possible that the liver status may not have been thoroughly investigated because of the unremarkable previous history of liver disease and lack of other symptoms in these variceal bleeding patients. Therefore, the possibility of HCC with PVT should be kept in mind in patients who presented with variceal bleeding, especially in the areas where HCC is prevalent.

Abdominal sonography is the first line diagnostic tool for HCC, especially in patients with poor general condition, which precluded the more invasive image studies.[13] Sonographically, the percentage of infiltrative type (28.6%) HCC in the variceal bleeding type HCC was higher than that observed previously in Taiwan (10.2%).[14] This was an important finding as sonographic diagnosis of the infiltrative HCC was more difficult.[15,16] Actually, the infiltrative HCC in two of our patients were missed in the initial sonography; instead, the computed tomography in these two patients showed ill-defined hypodense tumours without clear margin. As not all patients received computed tomography or angiography, it was possible that some infiltrative HCC were missed in these variceal bleeding patients. Sonographic operators should remember such difficulties and pitfalls in performing and interpreting the abdominal sonography. The portal vein should be worked-up more carefully, as it may be the only clue to the diagnosis of infiltrative HCC.[15] Although most of the HCC in our patients were large in size, the small HCC still could lead to extensive PVT resulting in subsequent variceal bleeding.

Liver biopsy was done in only two cases, and both showed Edmondson grade II trabecular HCC. The critical condition, bleeding tendency and massive ascites precluded liver biopsy in the remaining 12 patients. None of these 14 patients were operable because of PVT and/or decompensated liver cirrhosis. Only two patients could receive TAE for their HCC. However, not all the HCC in the remaining 12 patients were untreatable. Some of them died of massive variceal bleeding before they had the chance to receive therapy for their HCC.

Although endoscopic variceal ligation may be superior to endoscopic injection sclerotherapy in the management of variceal bleeding in patients with HCC,[17] these therapeutic procedures did not alter the course of patients with PVT.[18] This may be attributed to poor liver reserve and PVT.[18,19] The presence of HCC is one of the major determinants of post-therapeutic bleeding.[20] This also explained why our patients still died of massive variceal bleeding in spite of therapeutic intervention. None of the 14 HCC patients survived 1 year, and more than half of these patients died within 2 months. The prognosis in HCC presenting with the variceal bleeding seemed worse than that in our overall HCC. This extremely poor prognosis may be related to both the advanced stage of HCC and failure to control the variceal bleeding in our patients.

We concluded that variceal bleeding may be the first presentation in patients with HCC. The reason to emphasize such a presentation is that variceal bleeding might indicate the presence of HCC with PVT even in patients without a previous history of liver disease. Vigorous work-up to detect the existence of HCC with PVT in the variceal bleeding patients was warranted. The tumours in such patients might be the infiltrative type, and thus the portal vein should be carefully worked-up. Overall these patients have an extremely poor prognosis. In the management of patients with variceal bleeding, the possibility of HCC with PVT should not be overlooked, especially in areas where this cancer is prevalent.

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REFERENCES

1 Linsell DA, Higginson J. The geographic pathology of the liver cell cancer. In: Cameron HM, Linsell DA, Warwick GP, eds. *Liver cell cancer*. New York: Elsevier, 1976; 1–16.
2 Beasley RP. Hepatitis B virus as the etiologic agent in hepatocellular carcinoma: epidemiologic consideration. *Hepatology* 1982; **2** (Suppl.): 21–6.
3 Chen DS. Hepatitis B virus infection, its sequelae, and pre-

vention in Taiwan. In: Okuda K, Ishak KG, eds. *Neoplasms of the liver*. Tokyo: Springer-Verlag, 1987; 71–80.
4 Sung JL, Wang TH, Yu JY. Clinical study on primary carcinoma of the liver in Taiwan. *Am. J. Dig. Dis.* 1967; **12**: 1036–49.
5 Okuda K, Nakashima T. Primary carcinomas of the liver. In: Haubrich WS, Klaser MH, Roth JLA, Schaffner F. Bockus, eds. *Gastroenterology*, 4th edn. Philadelphia: WB Saunders, 1985; 3315–76.
6 Beppu K, Inokuchi K, Koyanagi N *et al.* Prediction of variceal hemorrhage by esophageal endoscopy. *Gastrointest. Endosc.* 1981; **27**: 213–18.
7 Shinagawa T, Ohto M, Kimura K *et al.* Real-time ultrasonographic diagnosis of hepatocellular carcinoma: correlation of echograms and histopathological findings. *Jpn. J. Gastroenterol.* 1981; **78**: 2402–11 (In Japanese with English abstract).
8 Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology* 1981; **80**: 800–9.
9 Inagaki Y, Unoura M, Kobayashi K. Clinical features and diagnosis of primary liver cancer. In: Tobe T, Kameda H, Okudaira M *et al.*, eds. *Primary liver cancer in Japan*. Tokyo: Springer-Verlag, 1992; 93–102.
10 Yeo W, Sung JY, Ward SC *et al.* A prospective study of upper gastrointestinal hemorrhage in patients with hepatocellular carcinoma. *Dig. Dis. Sci.* 1995; **40**: 2516–21.
11 Nakashima T. Vascular changes and hemodynamics in hepatocellular carcinoma. In: Okuda K, Peters RL, eds. *Hepatocellular Carcinoma*. New York: John Wiley and Sons, 1976; 169–203.
12 Cooney TG, Bauer DC, Knauer CM. Portal hypertension associated with hepatocellular carcinoma. *Am. J. Gastroenterol.* 1980; **74**: 436–8.
13 Sheu JC, Chen DS, Sung JL *et al.* Hepatocellular carcinoma: US evolution in the early stage. *Radiology* 1985; **155**: 463–7.
14 Wang KC, Jan CM, Chen CY, Wang LY, Wang WM, Tsai JF. Ultrasonographic pictures of primary and metastatic carcinoma of the liver. *J. Formosan Med. Assoc.* 1984; **83**: 658–67.
15 Sheu JC, Sung JL, Chen DS *et al.* Early detection of hepatocellular carcinoma by real-time ultrasonography. *Cancer* 1985; **56**: 660–6.
16 Tanaka S, Kitamura T, Ohshima A *et al.* Diagnostic accuracy of ultrasonography for hepatocellular carcinoma. *Cancer* 1986; **58**: 344–7.
17 Lo GH, Lai KH, Chang CF *et al.* Endoscopic injection sclerotherapy versus endoscopic variceal ligation in arresting acute variceal bleeding for patients with advanced hepatocellular carcinoma. *J. Hepatol.* 1994; **21**: 1048–52.
18 Lo GH, Lin CY, Lai KH *et al.* Endoscopic injection sclerotherapy versus conservative treatment for patients with unresectable hepatocellular carcinoma and bleeding esophageal varices. *Gastrointest. Endosc.* 1991; **37**: 161–4.
19 Ng WD, Chan YT, Ho KK, Kong CK. Injection sclerotherapy for bleeding esophageal varices in cirrhotic patients with hepatocellular carcinoma. *Gastrointest. Endosc.* 1989; **35**: 69–70.
20 Kokawa H, Shijo H, Kubara K *et al.* Long-term risk factors for bleeding after first course of endoscopic injection sclerotherapy: A univariate and multivariate analysis. *Am. J. Gastroenterol.* 1993; **88**: 1206–11.