

HEPATOCELLULAR CARCINOMA ASSOCIATED WITH LIVER ABSCESS

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Hepatitis B and hepatitis C are highly prevalent in Taiwan. Chronic hepatitis patients are at high risk of progression to liver cirrhosis and hepatocellular carcinoma (HCC). However, HCC in association with liver abscess is very rare. Accordingly, this study analyzed the characteristics of HCC patients with liver abscess to improve the differential diagnosis of this condition. From January 2005 to July 2007, the medical records of nine HCC patients (4 females, 5 males; mean age, 65.8 years) treated for abscess formation at Kaohsiung Medical University Hospital were retrospectively reviewed. Their clinical characteristics, images, management approaches and outcomes were analyzed. Fever and highly elevated alkaline phosphatase levels were noted in all patients. All aspirate cultures revealed *Klebsiella pneumoniae*. All of the cases of HCC were confirmed by cytology or pathology. The imaging studies, which included abdominal ultrasonography and computed tomography, revealed liver tumors in all patients. In some cases, lead-enhanced hypervascular areas were noted. The patients were treated with antibiotic therapy, transhepatic arterial chemoembolization, or surgery. The findings of this study indicate that focal liver inflammatory changes may mimic solid neoplasms. Differential diagnosis of HCC with abscess is extremely difficult and may require aspiration cytology or pathology.

Key Words: abdominal sonography, computed tomography, hepatocellular carcinoma, liver abscess, magnetic resonance imaging
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The incidence and mortality rate of hepatocellular carcinoma (HCC), one of the most common cancers worldwide [1], are rapidly increasing. Associated diseases include chronic viral hepatitis types B and C, which comprise approximately 75% of all HCCs [1,2], and liver cirrhosis (70–80% of all cases) [1,2]. Without

treatment, advanced HCC usually causes death within months, and long-term survival is rare [1]. Despite recent advances in diagnostic and therapeutic modalities, prognosis is usually poor, particularly in patients with coexisting liver cirrhosis.

In Taiwan, the incidence of HCC per 100,000 people is reportedly as high as 26 and 8 in males and females, respectively [3].

Pyogenic liver abscess usually occurs in patients with diabetes mellitus and malignancy [4]. Possible causes include hematogenous dissemination, ascending cholangitis and superinfection of necrotic tissue [5]. *Escherichia coli* is the most common bacterium



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worldwide. *Klebsiella pneumoniae* was first reported in Taiwan in the 1900s and now surpasses *E. coli* as the predominant isolate in patients with hepatic abscess [4–6].

An HCC manifesting as a liver abscess, due to either spontaneous liquefied necrosis of the tumor interior or biliary obstruction caused by a tumor fragment [7], is a condition rarely reported in the literature.

This study reviewed all HCC patients treated at this institution during the past 2.5 years and describes the characteristics of those who initially presented with liver abscess.

PATIENTS AND METHODS

This study retrospectively reviewed the medical records of 906 HCC patients treated between January 2005 and July 2007 at Kaohsiung Medical University Hospital (Kaohsiung, Taiwan). Data were collected for all treatment-naïve HCC patients who were initially diagnosed with liver abscess during hospitalization. All patient data, including clinical data, imaging studies and histology, were entered into a database for further analysis.

RESULTS

There were a total of nine patients (5 males, 4 females) who were initially diagnosed with liver abscess and in whom the final histology revealed HCC.

Patient characteristics

Nine of 906 (0.99%) patients had HCC with abscess presenting as pyogenic liver abscess. The mean age of the nine patients was 65.8 years (range, 52–80 years). Of the six hepatitis virus carriers, two, one, and three patients had hepatitis B, hepatitis C, and both hepatitis B and C, respectively. Only three patients were negative for both hepatitis B and hepatitis C. Three patients had diabetes mellitus. None of the patients were diagnosed with combined hepatolithiasis.

Manifestations

Symptoms included fever in all nine patients (with chills in 3), right-upper-quadrant pain in four, poor appetite in four, and fatigue in three. Other prominent signs included right-upper-quadrant tenderness in four, and jaundice (with indications including icteric sclera, tea-colored urine, or clay-colored stool) in two. No hepatomegaly or bulging abdominal mass was noted (Table 1).

Laboratory data

Of the nine patients, leukocytosis with left shift was noted in six. Anemia (defined as hemoglobin <13 g/dL in males and <12 g/dL in females) was noted in seven patients. The C-reactive protein levels (normal <5 µg/mL) were abnormal in all patients. Hyperbilirubinemia (normal 0.2–1.0 mg/dL) was noted in one patient. Six patients had hypoalbuminemia (normal 3.5–4.5 g/dL). In one patient, the prothrombin time was 4 seconds longer than normal (Table 2).

Mild-to-moderate abnormal serum aminotransferase level (<4-fold increase) and elevated serum

Table 1. Clinical characteristics of hepatocellular carcinoma patients with liver abscess

	Patient								
	1	2	3	4	5	6	7	8	9
Sex	M	M	F	M	F	F	M	F	M
Age (yr)	52	70	61	55	79	80	61	77	57
HBV	+	–	+	+	+	–	+	–	–
HCV	+	–	–	–	+	–	+	–	+
DM	–	+	–	–	+	–	+	–	–
Fever	+	+	+	+	+	+	+	+	+
Chills	–	–	–	+	+	–	–	–	+
RUQ pain	+	+	+	–	–	–	–	–	+
Poor appetite	–	–	–	+	+	–	–	+	+
Fatigue	–	–	–	+	+	–	–	–	+
Jaundice	–	–	–	+	–	–	+	–	–

HBV = hepatitis B virus; HCV = hepatitis C virus; DM = diabetes mellitus; RUQ = right-upper-quadrant.

Table 2. Laboratory data of hepatocellular carcinoma patients with liver abscess

	Patient								
	1	2	3	4	5	6	7	8	9
WBC (/μL)	12,670	9,370	7,920	10,340	8,740	22,570	9,890	17,050	10,870
Neutrophil (%)	79.4	78	67.6	87	78.2	92.8	78	86.1	70.1
Hemoglobin (g/dL)	13.9	12	11.4	14.2	10.5	7.8	10.7	7.6	10.8
CRP (μg/mL)	14.2	9.4	66.9	285.2	118.4	211.6	122.1	141.0	198.3
Total bilirubin (mg/dL)	0.6	0.59	1.72	2.09	0.85	1.74	4.84	0.42	0.78
Albumin (g/dL)	3.59	3.38	3.59	2.5	3.62	2.35	2.77	2.81	3.47
Prothrombin time (sec)	12.1	11.6	14.0	15.9	11.9	12.8	13.0	13.0	12.5
PT-INR	1.24	1.02	1.51	1.84	1.27	1.25	1.26	1.28	1.33
ALT (IU/L)	44	35	50	53	43	56	99	34	29
AST (IU/L)	49	35	52	66	36	52	123	41	25
ALP (IU/L)	170	141	27	134	187	345.7	360	127.7	122
α-fetoprotein (ng/mL)	3.9	154.9	5.6	11.2	5.12	4.3	98.4	3.1	2.7

WBC=white blood cell count; CRP=C-reactive protein; PT-INR=prothrombin time-international normalized ratio; ALT=alanine transaminase; AST=aspartate transaminase; ALP=alkaline phosphatase.

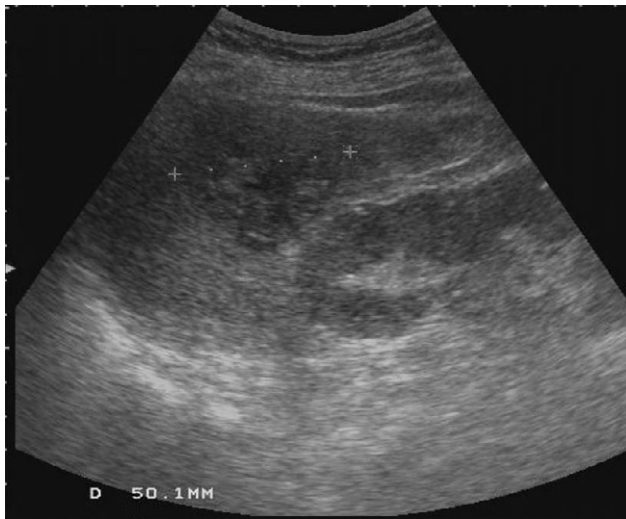


Figure 1. Abdominal sonography shows hepatocellular carcinoma with liver abscess: an irregular 5-cm mosaic echoic mass was found in segment 6 of the liver.

alkaline phosphatase level were noted in eight of the nine patients (Table 2).

Work-up of liver abscesses

All patients underwent ultrasonography (US; Figure 1) and computed tomography (CT; Figure 2) examinations to detect the presence of abscess and characteristics of the liver (Table 3). Abscess aspiration and culture collection were also performed. All abscess cultures were positive for *K. pneumoniae*. All patients underwent antibiotic therapy, and none required drainage tube insertion.

Characteristics of HCC

Tumor size was 3–13 cm (mean, 5 cm). In eight of the nine patients, liver abscess and HCC were both diagnosed during the initial hospitalization. One patient initially diagnosed with abscess suffered one recurrence but, after the patient underwent resection of the lesion, the final diagnosis was HCC with liver abscess.

Management of HCC and outcomes

After antibiotic treatment of the liver abscess, one patient received conservative treatment due to hepatic failure. Two patients underwent tumor resection after antibiotic treatment, and neither revealed evidence of recurrence during follow up. Most (6) patients underwent transhepatic arterial chemoembolization after completing antibiotic therapy. One of the nine patients died of sepsis after undergoing three transhepatic arterial chemoembolization treatments.

DISCUSSION

Patients with liver abscess usually present with fever, chills, anorexia, fatigue, or other symptoms such as nausea, vomiting, right-upper-quadrant pain, diffuse abdominal pain, pleuritic chest pain, and jaundice [8]. Fever, the most common symptom, reportedly occurs in 70–95% of cases [8]. All patients in the current study were febrile. Some also exhibited right-upper-quadrant pain, fatigue, and jaundice. The most common laboratory finding in these patients is leukocytosis,

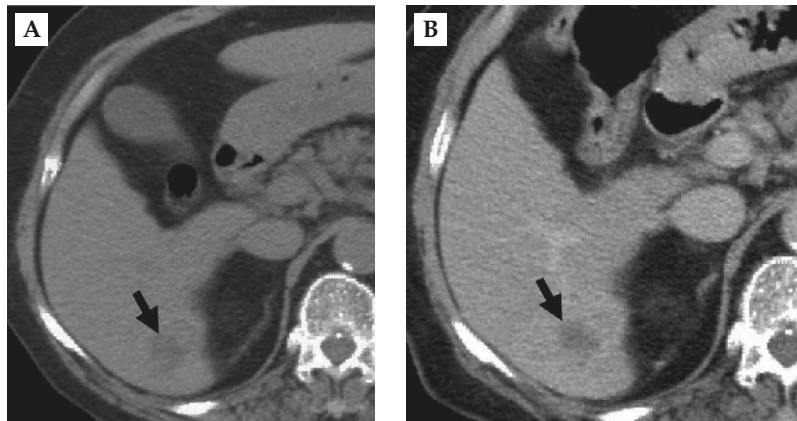


Figure 2. Abdominal computed tomography shows hepatocellular carcinoma with liver abscess. (A) Unenhanced computed tomography revealed an internal heterogenic attenuated tumor with an irregular and unclear margin (arrow) in segment 6 of the liver. (B) No obvious internal enhancement was noted after contrast infusion (arrow).

which reportedly occurs in 70–82% of patients [8]. Alkaline phosphatase levels 2–3 times the upper limit of normal are also common [6,8]. Elevated transaminase levels and hypoalbuminemia are also commonly observed. All of the patients in the current study exhibited leukocytosis and high alkaline phosphatase levels [9].

An abscess-like clinical presentation, particularly with the coexistence of tumor necrosis, is one symptom of HCC [7,10]. According to Smalley et al, these features occur in approximately 25% of all HCC patients with a non-cirrhotic liver [11]. The literature also describes several cases of abscess-like clinical symptoms [7]. One explanation for these similarities is neoplasm-associated granulocytosis resulting from granulopoietin production by tumor cells as well as pyrogen production by malignant tumor cells or by macrophages followed by tumor necrosis [7,12].

For early diagnosis and differential diagnosis of liver abscess, careful imaging of manifestations and their characteristics is essential. In this study, CT scans revealed low attenuation in all liver abscesses, and 91.7% of the enhanced lesions had a rim-shaped enhancement in the abscess wall, as described elsewhere [9]. Honeycomb-like, grid-like or strip-like enhancements reportedly occur in 75% of cases [9]. The CT findings of hepatic abscess are usually unremarkable, and diagnosing abscess is rarely difficult [9].

An HCC typically presents as an intense enhancement in the arterial phase and as a contrast washout in the subsequent venous contrast phase [10]. Well-defined margins are more common in large HCC

lesions than in smaller tumors [10]. The HCC is likely to present as a dominant mass with underlying liver damage characterized by smooth and encapsulated margins, necrosis and hypervascularity [10]. Recognizing the enhanced pattern characteristics of HCC is essential for accurate diagnosis. Distinguishing the hypervascular malignant area from the abscess lesion is also important.

A US image of liver abscess usually shows a low-echoic to mixed-echoic lesion [13,14]. The margin may be blurred or irregular due to inflammation of surrounding areas [13,14]. During the early stage, mixed-echoic parenchyma mass lesions are common, but significant tissue liquefaction is rare [13,14]. Following the course of inflammation, sonography may reveal a low-echoic mass lesion. However, HCCs of <3 cm in diameter usually appear hypoechoic without posterior enhancement whereas larger lesions, which are often necrotic and fibrotic, exhibit a more heterogeneous (mosaic) pattern [10]. Accurate differential diagnosis of HCC is essential in endemic areas such as Taiwan. Color Doppler US or even contrast injection are often helpful.

US findings of HCC with abscess may reveal single or multiple carcinomas, and either lobe may be involved. The size also varies. US can reveal the features of the liver abscess and, in some cases, those of the tumor itself. In the cases reported here, enhanced abdominal CT revealed that the area affected by the tumor was in the advanced arterial phase, which enabled the differential diagnosis of HCC alone versus liver abscess alone. Color Doppler or

Table 3. Imaging results for hepatocellular carcinoma patients with liver abscess

		Patient							
		2	3	4	5	6	7	8	9
Number	1	Multiple	Single	Single	Single	Multiple	Single	Single	Single
Location		Diffuse	Right lobe	S5	S6	S8	S6	S3	S3
Tumor size		>10 cm	5 cm	3 cm	3 cm	5 cm	3.2 cm	5 cm	9.5 cm
Sonographic features		Low peripheral ring, mixed-echoic tumor, low-echoic and central low-septated echoic tumor, homogeneous echogenicity	Isoechoic tumor, poorly defined margin	Mixed-echoic tumor, low peripheral ring	Low-echoic tumor, poorly defined margin	Mixed-echoic tumor, low peripheral ring	Low-echoic tumor, irregular margin	Mixed-echoic tumor, irregular margin, low periphery	Low-echoic tumor, irregular margin
CT features		Diffuse isoechoic to low-density tumor in precontrast and venous phase, high-density tumor in arterial phase	Low-attenuation lesion, blurred margin, unenhanced on contrast CT	Low-attenuation lesion, poorly defined, unenhanced on contrast CT	Low-attenuation lesion, poorly defined, unenhanced on contrast CT	Low-attenuation lesion, irregular margin, central liquefaction	Low-attenuation lesion, irregular margin, unenhanced on contrast CT	Low-attenuation lesion, unenhanced on contrast CT	Wall-thickened and septated mass with interior fluid density
Aspiration features		Pus-like sticky fluid	Pus-like sticky fluid	Pus-like sticky fluid	Pus-like fluid with mild particles	Pus-like sticky fluid	Pus-like sticky fluid	Pus-like sticky fluid	Pus-like sticky fluid

S5 = segment 5; S6 = segment 6; S8 = segment 8; S3 = segment 3; CT = computed tomography.

contrast-enhanced imaging studies are essential to diagnose HCC. Detailed examination of the aspirate is also needed to identify malignant cells.

An abscess-like presentation is one marker for HCC, particularly in patients with tumor necrosis. Distinguishing between HCC and liver abscess without aspiration findings and using clinical presentations alone is extremely difficult. In this study, liver tumor aspiration frequently reveals not only pus, but also HCC tissue, which was further confirmed by pathology. The aspiration procedure is essential to diagnose HCC.

Liver abscess and hepatic tumor necrosis are difficult to distinguish by clinical symptoms, serology examination and imaging studies. Verification by punctate pathology is essential in HCC-endemic areas of Taiwan.

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肝細胞癌併發肝膿瘍

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B 型肝炎和 **C** 型肝炎在台灣是較普遍的。病人有較高的危險性進展成肝硬化和肝細胞癌。然而，肝癌合併肝膿瘍的發生則極少見。藉由分析這些病人的臨床特徵來鑑別診斷肝細胞癌及肝膿瘍。從 2005 年一月至 2007 年七月共有九名肝癌併發肝膿瘍的病人。分析其臨床表徵、影像學特性、治療和癒後。共四名女性及五名男性，平均年齡 65.8 歲。發燒及明顯升高的鹼性磷酸酶在所有病人都可發現。肝膿瘍抽吸的細菌培養結果均為克雷白氏肺炎菌 (*Klebsiella pneumoniae*)，而肝細胞癌均需要由細胞學或病理診斷。影像學的檢查上，包含腹部超音波、腹部電腦斷層掃描均能檢出肝腫瘤，其中某些病例更能在顯影劑注射後顯現出早期顯影 (early enhance) 的肝癌病灶。治療方面則包含了抗生素、肝腫瘤動脈化學栓塞、或手術切除。肝臟局部發炎性的變化可能會和實質性腫瘤相似。臨床上要做準確的鑑別診斷較為困難，尤其是併發肝膿瘍的肝細胞癌。最後的診斷通常仍須依靠肝腫瘤抽吸或病理檢查。

關鍵詞：腹部超音波影像，電腦斷層掃描影像，肝細胞癌，肝膿瘍，核磁共振造影
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