Original Research Article

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Clinical research of primary liver cancer mimicking liver abscess

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ABSTRACT

Background: Aiming at diagnosing at an early stage, minimizing the misdiagnosis rate and improving the prognosis, the author has investigated the clinical characteristics, diagnosis and treatment of primary liver cancer mimicking liver abscess with a summary and discussion.

Methods: All of the 11 cases of primary liver cancer mimicking liver abscess, diagnosed during January 2009 to December 2015, were retrospectively viewed in terms of clinical manifestations, laboratory tests, radiological feature, diagnosis and treatment. And statistic analysis was made in all aspects mentioned above with that of pyogenic liver abscess and other types of liver cancer diagnosed in the corresponding period.

Results: The clinical manifestations of the 11 cases were mostly characterized by fever, abdominal pain and weight loss. There was no significantly statistic difference between the study group and any of the three matched groups in underlying disease and lab results. All of the 11 patients were treated with enhanced antibiotics as basic therapy. Furthermore, eight cases accepted surgical operation, among them, one object underwent puncture and drainage of the liver abscess by ultrasound (PDLA) twice pre-operation, one object underwent PDLA and hepatic arteriography pre-operation and death in hospital post-operation, one object suffered myocardial infarction post-operation. In addition, three cases received conservative treatment only, in which, one object died in hospital.

Conclusions: It is difficult to distinguish primary liver cancer mimicking liver abscess from pyogenic liver abscess as there are no specific clinical manifestations and laboratory findings which is prone to leading to misdiagnosis. What's worse, the prognosis is so poor that high alert and close follow-up are required as well as early diagnosis and treatment.

Keywords: Differential diagnosis, Fever, Liver tumor, Pyogenic liver abscess

INTRODUCTION

Primary liver cancer (PLC) is the second leading cause of cancer-related death of men worldwide, there are nearly 782,500 new liver cancer cases and 745,500 deaths occurred worldwide each year, while half the total number of new cases and deaths occurred in China. 1,2 Liver cancer was onset occult, with rapid progression and

no specificity on the clinical characteristics. While partial cases are characterized by fever or hyperpyrexia as the initial or only manifestation, which are difficult to distinguish from pyogenic liver abscess (PLA) and associating with poor prognosis consequently. This article has investigated the clinical characteristics, diagnosis and treatment of primary liver cancer mimicking liver abscess with a summary and discussion,

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aiming at diagnosing at an early stage, minimizing the misdiagnosis rate and improving the prognosis.

METHODS

In this retrospective case-control study, we indentified 11 cases (study group) who had been hospitalized owing to a diagnosis of pyogenic liver abscess and treated with puncture and drainage of the liver abscess (PDLA) or surgical drainage during January 2009 to December 2015. and all the 11 case were finally confirmed as primary liver cancer according to the pathological and later radiological finding. For each case in the study group, 12 cases of other PLA or PLC patients were randomly selected who were diagnosed in the corresponding period and with matched age and gender and statistic analysis was made in terms of clinical characteristics, laboratory tests. There are three control groups including PLA group (group B), common PLC group (group C) and PLC with fever group (group D). While the PLC with fever group was characterized by fever (≥38°C), but with typical clinical and radiological finding and had not been misdiagnosed as pyogenic liver abscess. And the residual primary liver cancer patients belong to the common PLC group except for the patients in the study group and group of PLC with fever. This study was approved by the Ethics Committee of Chongqing Medical University.

Statistical analysis

Continuous variables are expressed as mean±SD, normal distribution data were analyzed with completely random

design analysis of variance, comparisons among groups were performed with Bonferroni test and Games-Howell test. While non-normal distribution data analyzed with non-parametric tests (Kruskal-Wallis H test). Categorical data were compared using chi-square or Fisher's exact test as indicated. A P-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL).

RESULTS

Patients clinical characteristics

The 11 patients in the study group ranged in age from 33 to 81 years, with a mean age of 59.36±13.39 years, included seven men and four women. There were five cases both for hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHCC), one case for combined hepatocellular carcinoma and intrahepatic cholangiocarcinoma (cHCC-CC). A total of five (45.5%) patients had hepatitis-B virus (HBV), one (9.1%) patient had diabetes mellitus (DM), three (27.3%) patients had liver cirrhosis, and three (27.3%) patients had cholelithiasis. The prevalence of HBV and cirrhosis were significant higher in the study group (group A) than PLA group (group B) only, and there were no significant differences in underlying DM or cholelithiasis. But study group (group A) compared with common PLC group (group C) or PLC with fever group (group D), no significant differences had been found in underlying four diseases (Table 1)

Table 1: Clinical characteristics	or study	group and	three matched	groups.
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	Study group (group A; n = 11)	PLA group (group B; n = 44)	Common PLC group (group C; n = 44)	PLC with fever group (group D; n = 44)	P	
-:	n (%)	n (%)	n (%)	n (%)		
Sex					_	
Female	4 (36.4)	16 (36.4)	16 (36.4)	16 (36.4)	1.00	
Male	7 (63.6)	28 (63.6)	28 (63.6)	28 (63.6)		
Age/year	59.36±13.39	58.48±15.03	61.09±11.93	56.05±11.45	0.220	
<65	7 (63.6)	28 (63.6)	25 (56.8)	30 (68.2)	0.339	
≥65	4 (36.4)	16 (36.4)	19 (43.2)	14 (31.8)	0.744	
HBV ^b	5 (45.5)	3 (6.8) a	20 (45.5)	36 (81.8)	< 0.001	
DM	1 (9.1)	13 (29.5)	6 (13.6)	10 (22.7)	0.222	
Cirrhosis	3 (27.3)	3 (6.8) a	9 (20.5)	25 (56.8)	< 0.001	
Cholelithiasis	3 (27.3)	20 (45.5)	10 (22.7)	7 (15.9)	0.015	

HBV, hepatitis B virus; HCV, hepatitis C virus; DM, diabetes mellitus; Compared with study group, significant differences had been found (P<0.05); HCV had not included in the analysis because only group D had one case.

Clinical manifestations

Followed by abdominal pain (n = 9), weight loss (n = 6), fatigue (n = 6), anorexia (n = 5), nausea (n = 4), vomiting (n = 2), diarrhea (n = 1), chills (n = 1) and jaundice (n = 1)

1), fever (n = 11) was the most common symptom, among which, five cases presented with continuous hyperpyrexia (up to $40.0~^{\circ}$ C). While the most frequent physical sign was right-upper-quadrant abdominal tenderness.

Laboratory characteristics

The laboratory data on admission of patients in study group are shown in Table 2 and 3. We can see that the leukocytosis or neutrophilia increased in 7 patients, while the serum procalcitonin (PCT) was nearly normal. 8 patients had anemia, with the mean hemoglobin of 112.73±18.13 g/L, thrombocytosis or thrombocytopenia

were both noted in 2 patients respectively. 10 patients had hypoalbuminemia, with a mean hypoalbuminemia of 32.12±5.1 g/L. The serum alpha-fetoprotein (AFP) and Carbohydrate antigen 19-9 (CA19-9) level were normal in most patients while elevated AFP and CA19-9 level were noted in only one patient and four patients respectively.

Table 2: Comparison of laboratory	data between study grou	p and three matched groups.

Lab data	Study group (group A n = 11)	PLA group (group B n = 44)	Common PLC group (group C n = 44)	PLC with fever group (group D n = 44)	P
WBC (×10 ⁹ /L)	14.28±14.83	11.71±5.79	7.63±3.74	8.33±4.35	0.001
Neutrophil (%)	78.46 ± 10.15	82.87±8.09	70.56±11.82	74.47±9.95	< 0.001
HB (g/L)	112.73±18.13	107.25±22.80	124.23±19.89	115.57±23.54	0.005
Platelet(×10 ⁹ /L)	198.36±118.08	249.95±123.04	188.50±83.90	164.05±81.98	0.002
ALT (U/L) b	65.64±78.79	61.91±47.60	76.64±136.15	69.95±64.54	0.453
AST(U/L) ^b	48.55±51.57	74.09±89.98	75.30±137.92	130.11±144.53 a	< 0.001
ALP (U/L) ^b	277.27±194.58	196.03±130.76	262.09±317.35	238.18±159.04	0.258
TB (μmol/L) b	12.55±7.02	14.16±9.31	47.51±74.44	33.18±36.51 a	< 0.001
DB (μmol/L) b	7.79±6.05	9.12±7.30	33.97±59.94	21.31±30.47 a	< 0.001
Albumin (g/L)	32.12±5.11	30.28 ± 5.17	37.93±6.06 a	32.22±4.67	< 0.001
PT (seconds)	14.67±1.98	14.70±1.18	13.81±2.08	15.08±1.84	0.009
AFP>20 (μg/L)	1 (9.1%)	0 (0%)	12 (27.3%)	32 (72.7%) ^a	< 0.001
Ca19-9>37(U/ml)	4 (36.4%)	6 (13.6%)	20 (45.5%)	4 (9.1%)	< 0.001
dmax (cm)	7.72±3.90	7.34±3.01	4.76±2.20	8.20±3.73	< 0.001

WBC, white blood cell; HB, Hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin; PT, prothrombin time; AFP, alpha-fetoprotein; CA19-9,carbohydrate antigen 19-9. a Compared with study group, significant differences had been found (P<0.05).

b Data were non-normal distribution and analyzed with non-parametric tests (Kruskal-Wallis H test).

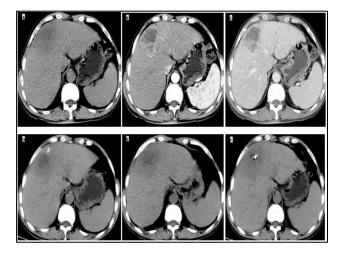


Figure 1. CT images of patient 3, (the first admission). A: plain CT scan image, B: Contrast-enhanced CT image (arterial phase), C: Portal venous phase, 07-15. D: 5 days after PDLA for the first time (07-22). E: 16 days after PDLA for the first time (08-03). F: 5 days after PDLA for the second time (08-10).

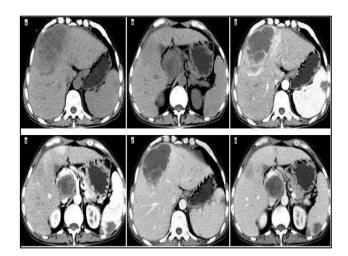


Figure 2. CT images of patient 3 show hypodense lesion with ring enhancement in the liver and behind the hepatoduodenal ligament (The second admission, 09-11).

Compared with three control groups respectively, no significant differences have been found in white blood cell counts, neutrophil percentage, hemoglobin, platelet

counts, serum alanine transaminase level, alkaline phosphatase level, CA19-9 level, or prothrombin time. However, significant differences were noted in AFP, serum aspartate aminotransferase level, total bilirubin, direct bilirubin between study group and PLC with fever group (P <0.05), and in albumin level between study group and common PLC group (P <0.05)

Table 3: Laboratory data of 11 cases in the study group.

	Normal						Patient					
	range	1	2	3	4	5	6	7	8	9	10	11
Sex		F	M	M	M	F	M	F	M	M	F	M
Age (year)		60	76	58	81	61	33	65	65	59	49	46
WBC(×10 ⁹ /L)	3.5-9.5	19.6	6.45	16.01	3.19	10.78	56.05	16.84	7.73	6.67	9.13	4.65
Neutrophil (%)	45-75	90.4	64.9	83.1	82.8	77.9	92.3	90.6	76.1	70	65.7	69.3
HB (g/L)	130- 175 ^a	81	132	138	113	113	121	108	92	118	93	131
Platelet(×10 ⁹ /L)	100- 300	428	109	196	62	402	81	178	219	155	152	200
ALT (U/L)	5-40	28	29	66	15	49	281	30	15	20	130	59
AST (U/L)	5-40	29	32	39	14	21	189	22	16	28	93	51
ALP (U/L)	45-135	135	120	138	157	597	509	153	537	139	427	138
TB (μmol/L)	2.3- 20.4	6.6	9.3	14.3	14.6	12.3	14.1	9.2	14	8.1	31	4.6
DB (μmol/L)	0-11	4.6	4.3	7.7	9.4	6.6	9.4	5.4	8.4	3.1	24.5	2.3
Albumin (g/L)	40-55	26.1	31.2	32	33.3	37.1	28.9	31.2	30.5	37.4	24	41.6
PT (seconds)	11-14.5	15.9	16.4	14.6	15.2	12.7	18.5	16.1	12.8	11.8	13.3	14.1
AFP (μg/L)	0-20	3.74	3.1	1.77	5.14	2.92	3.81	11.8	29.4	3.45	3.7	13.21
Ca19-9 (U/ml)	0-37	2.24	2.74	5.53	>1000.0	>1000.0	1.51	7.2	41.12	>1000.0	26.38	8.08
PCT (ng/ml)	0.02-0.5	0.15	0.41	0.26	0.13	0.59			0.36			0.28

WBC, white blood cell; HB, Hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin; PT, prothrombin time; AFP, alpha-fetoprotein; CA19-9, carbohydrate antigen 19-9; PCT, procalcitonin. a Normal range for men, while 115-150 g/L was normal range for women.

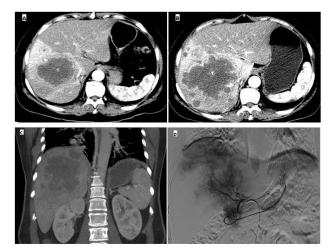


Figure 3. CT and arteriography images of patient 5. A: Contrast-enhanced CT image (arterial phase) at the first admission (10-08). B, C: Contrast-enhanced CT (arterial phase) and three dimensional reconstruction images at the second admission (11-12). D: Hepatic arteriography image at the first admission (10-08).

Management and outcome

Misdiagnosed as pyogenic liver abscess, all of the 11 patients were treated with enhanced antibiotic therapy, such as meropenem, imipenem and vancomycin etc. Furthermore, eight cases accepted operation, among them, one object underwent PDLA twice pre-operation, one object underwent PDLA and hepatic arteriography pre-operation and died in hospital post-operation, one object suffered myocardial infarction post-operation. In addition, three cases received conservative treatment only, among which, one object died in hospital.

Among them, three cases had been previously admitted to hospital twice with misdiagnosis, including case 3, 5 and 11. The case 3 patient underwent PDLA twice during the first admission, but only a small amount of yellow pus was drained out. After close follow-up without obvious change in size of liver mass (figure 1), the patient automaticly discharged from hospital and was admitted in again with recurrent hyperpyrexia one month later. During the second hospitalization, the liver mass was found to be significantly larger than before, and one unexpected mass behind the ligamentum hepatoduodenale emerged (figure 2). Subsequently,

exploratory laparotomy and surgical drainage were carried out. As a result, a large amount of purulent necrosis was found which further suported the diagnosis of abscess. However, the pathological finding finally revealed poorly differentiated hepatocellular carcinoma. The case 5 patient underwent PDLA and hepatic arteriography during the first admission, while no obvious pus extraction was found after puncture. Nevertheless, a hypovascular mass without tumor like vessels was observed during the hepatic arteriography,

and the patient was discharged after symptomotic improvement. One month later, again, the patient was admitted to hospital with recurrent fever and abdominal pain. And subsequent exploratory laparotomy was carried out after the liver mass had been found to be significantly larger than before(figure 3). But it was too late to complete radical resection as there had been multiple intra-hepatic metastatic foci already, and the patient died 23 days after surgery in hospital

Table 4: Related case reports of primary liver cancer mimicking liver abscess.

Author (years)	HCC cases	Mean age (years)	Fever cases	WBC elevated cases	AFP or Ca19-9 elevated cases	HBV/HCV/ Cirrhosis cases	Tumor diameter (cm)	Surgery	60-days mortality (%)
Li et al ⁴	5 a	59	9	9	7	3/1/1	7.9	7	33.3
Lin et al ³	698	61	-	-	_	136/100/247	-	-	14.5
Huang et al ⁵	9	65.8	9	6	2	2/1/- b	5.0	2 (TACE 6 cases)	-
Yeh et al ⁶	10	57.7	10	10	-	-	7.5	7	20
Okuda et al ⁷	5	58.6	5	5	1	0/-/1	-	2	40

TACE, transcatheter arterial chemoembolization.; a There were four cases of IHCC besides; b Three cases combined HBV with HCV in addition

DISCUSSION

Fever was a normal symptom in PLC patients, but rarely is the patient characterized by fever or hyperpyrexia as the initial or only manifestation, in that case, it is apt to be misdiagnosed as pyogenic liver abscess. Among the 32,454 patients with initial diagnosis of pyogenic liver abscess at admission in Taiwan, extracted by Lin et al, a total of 698 (2.15%) patients had turned out to be primary liver cancer.³ With related case reports shown in Table 5, it warned no rareness of this type of primary liver cancer, so highlightened alertness and close follow-up are strongly required.

The primary liver cancer mimicking pyogenic liver abscess including our 11 cases are prone to be misdiagnosed. Some factors such as non-specific symptoms, lack of independent risk factor for primary liver cancer et al, may lead to the misdiagnosis. Consistent with the result of Lin et al, the prevalence of HBV and liver cirrhosis were significantly higher in the study group than that of PLA group (P <0.05), which supported them to be the independent risk factor for primary liver cancer, but the former found that the 2 indicators were significantly lower in the study group than that of common PLC group (P<0.05), indicating that primary liver cancer patients without risk factor are more likely to be misdiagnosed.3 But the conclusion has not been reached in this study because of insufficiency of cases. No specific laboratory findings in study group patients were found, nor was the statistic difference among the comparison between the study group and other 3 groups respectively. Besides, the imaging of this kind of PLC looks exactly like that of unliquefied liver abscess. So the differential diagnosis cannot be made upon the laboratory and imaging findings. However, we found that the patients with fever were all in the advanced stage and it was very common to see metastases intrahepaticly or all over. Though CT and MRI are most commonly applied for detection of PLC due to the high sensitivity, but its role in differentially diagnosing PLC mimicking PLA from PLA was limited, owing to untypical radiological features.

A majority of tumors in sutdy group are characterized by peripheral or ring enhancement, central septum, and low density or fluid density without enhancement in central part of tumor, and the radiological features mentioned above attribute to central degeneration, necrosis or liquefaction of tumor. So regular examination and close follow up are proposed. Furthermore, it is worth mentioning that hepatic arteriography cannot identify primary liver cancer occasionally, such as the case 5. In that case, exploratory laparotomy or fine needle aspiration biopsy should be scheduled. But the false negative rate of biopsy was higher than that of normal primary liver cancer, because of the central necrosis or liquefaction of tumor. And a "real pyogenic liver abscess" might form after the secondary infection of necrotic tumor tissue, thus positive finding might be found in blood culture and pus culture as Huang et al reported, which may easily lead to misdiagnosis.⁵ Study by Kao et al has reported that patients with pyogenic liver abscess have significantly higher risks of developing primary liver cancer compared with that of the general population on follow up. After a median (±s.d.) follow-up of 3.33±3.45 years, 56 liver cancer cases were identified among 1257 patients who had been diagnosed with pyogenic liver abscess.⁵ The highest standard incidence ratio (SIR) occurred within 90 days of follow up (257.28; 95% CI, 186.17-346.56). That means the highest risks of developing primary liver cancer are within 90 days of follow-up, but there is a controversial question that whether primary liver cancer occurred first or the pyogenic liver abscess within the 90 days, namely that primary liver cancer just presented and be misdiagnosed as pyogenic liver abscess initially. Regardless of whichever occurred first, intensive follow up within 90 days could contribute to early detection of primary liver cancer, such as the case 3, case 5 and case 11, whose accurate diagnoses were made till the second admission within 30-60 days after the first admission. These patients are with poor prognoses and high mortality rates. The 60day mortality rate of 698 patients as Lin et al reported was 14.5%, and 30-40% as Li et al reported.^{3,4,7} We found that 2 patients died in hospital among 11 cases and the in-hospital mortality was 18.2% in this study.

CONCLUSION

It is difficult to distinguish primary liver cancer mimicking liver abscess from pyogenic liver abscess as there are no specific clinical manifestations and laboratory findings which is prone to leading to misdiagnosis. What's worse, the prognosis is so poor that high alert and close follow-up are required as well as early diagnosis and treatment.

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Ethical approval: The study was approved by the

institutional ethics committee

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