

# Pyogenic Liver Abscess Associated with Septic Pulmonary Embolism

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**Background:** Septic pulmonary embolism (SPE) is one of the metastatic foci of pyogenic liver abscess. The purpose of this study was to investigate the clinical presentations of, and management options for patients with pyogenic liver abscess complicated with SPE.

**Methods:** A retrospective chart review was conducted from January 1, 1999 to December 31, 2005 inclusively, in a medical center in northern Taiwan. We collected and analyzed the clinical presentations, diagnostic modalities, treatment programs and prognoses for all pyogenic liver abscess patients with SPE.

**Results:** The association between liver abscess affected with the complication of SPE and diabetes mellitus was significant. There were 9 patients who had pyogenic liver abscess with SPE. Abnormal chest radiograph (CXR) findings with multiple ill-defined peripheral round densities were noted in all patients. Seven patients were diabetic, fever occurred in 5 patients, respiratory symptoms were noted in 6 patients, and abdominal pain occurred in 3 patients. Endophthalmitis coexisted in 3 patients, meningitis in 1 patient, and necrotizing fasciitis in 2 patients. Microbiological studies revealed *Klebsiella pneumoniae* in 9 patients. Computed tomography (CT) demonstrated metastatic nodules in both lung lobes, some of which featured cavitation, in all 9 patients. Three patients soon advanced to acute respiratory failure, and later died due to acute respiratory distress syndrome and/or septic shock. The remaining 6 patients survived without complication during their hospital course.

**Conclusion:** There is diagnostic value in performing a chest CT scan in diabetic patients who have liver abscess plus abnormal CXR findings with multiple ill-defined peripheral round densities, in order to detect SPE, which has a relatively poor outcome in patients with liver abscess. [*J Chin Med Assoc* 2008;71(9):442–447]

**Key Words:** diabetes mellitus, liver abscess, septic pulmonary embolism

## Introduction

There is a rather high prevalence of liver abscess amongst diabetic patients in Taiwan, and a number of such cases involve the complication of septic pulmonary embolism (SPE).<sup>1–3</sup> SPE is an uncommon but serious disorder that has been associated with certain risk factors for adult patients, such as intravenous drug use, right-side bacterial endocarditis, pelvic thrombophlebitis, the presence of an indwelling catheter, and suppurative processes in the head and/or neck.<sup>4</sup> The most common pathogens associated with such a condition are Gram-positive cocci, including *Staphylococcus*

*aureus* for intravenous drug users, and *Staphylococcus epidermidis* and *Streptococcus spp.* for patients afflicted with thrombophlebitis.<sup>4,5</sup> Infections by Gram-negative organisms such as *Escherichia coli*, *Pseudomonas spp.*, *Klebsiella spp.* and *Proteus spp.*, however, may also occur amongst those who suffer from SPE.<sup>5</sup> The risk factors and clinical presentations of SPE are different from those of venous thromboembolism.<sup>6</sup> Patients afflicted with SPE generally present with an insidious onset of fever, cough or hemoptysis; some patients experience complications such as lung abscess, empyema, bronchopleural fistula, and massive hemoptysis.<sup>7</sup> In general, the clinical presentations of SPE are nonspecific, which



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may result in delayed diagnosis of the condition if appropriate radiographic studies are not promptly arranged.<sup>4</sup> The present study analyzed the clinical presentations, diagnostic tools, therapeutic modalities and prognoses for patients with liver abscess and SPE.

## Methods

We conducted a retrospective analysis of patients with liver abscess and SPE treated at a 2,800-bed medical center in northern Taiwan from January 1, 1999 to December 31, 2005. For the purposes of this study, pyogenic liver abscess was diagnosed if 1 or more areas of hepatic echolucency using ultrasonography or 1 or more hypodense areas of the liver using computed tomography (CT) were observed, and after obtainment of a positive culture from either blood or percutaneous aspiration of the liver abscess or septic metastases.<sup>1</sup> A case definition of SPE was: (1) the presence of lung abscess, multiple round or wedge-shaped dense entities located in the lung periphery; (2) the presence of active extrapulmonary infection as a potential embolic source; and (3) resolution of pulmonary lesions after administration of antimicrobial agents, clearly indicating an infectious cause.<sup>4</sup> In a situation of rapid progression of lung infiltration, SPE was also suggested by the clinical presentation of infectious disease and the results of bacterial culture, either from the embolic source or metastatic sites. We reviewed 831 cases of liver abscess, of which 581 cases had no other intra-abdominal infection and were considered as cases of primary liver abscess. Four hundred and eighteen patients with definite pathogens were considered to

have pyogenic liver abscess and were enrolled in the analysis. An abdominal CT scan was performed in 365 of the 418 patients to confirm the diagnosis of primary pyogenic liver abscess. The rest of the patients were diagnosed as primary pyogenic liver abscess cases according to the results of abdominal ultrasonography and whether there was a lack of clinical evidence of other primary infection sources. Twenty-eight patients with pyogenic liver abscess had septic metastases. All data were obtained by reviewing patients' histories, conducting a physical examination and microbiological studies, administering a chest radiograph (CXR) or CT, giving treatment, and prognosis.

Unpaired *t* tests and Fisher's exact tests (Sigmastat version 3.0; SPSS Inc., Chicago, IL, USA) were used to compare the data obtained from patients with and without septic metastases. This study followed the principles outlined in the Declaration of Helsinki.

## Results

### Patients

The general and clinical data of the patients with and without septic metastases are shown in Table 1. The association between liver abscess complicated with septic pulmonary embolism and diabetes mellitus was significant ( $p=0.012$ ). Although insignificant, patients with septic pulmonary embolism had a trend of increased chest complaints including cough and dyspnea, and higher rates of complication and mortality when compared to patients without septic metastases.

Nine patients (7 males) met the diagnostic criteria of pyogenic liver abscess and SPE, a mean age of

**Table 1.** Clinical characteristics of patients with and without septic metastases

	Group A	Group B	Group C
	Without septic metastases (n = 390)	With non-lung septic metastases (n = 19)	With septic pulmonary embolism (n = 9)
Mean age, yr	64.1	64.2	56.0
Male sex, n (%)	263 (64.44)	13 (68.42)	7 (77.78)
Diabetes mellitus, n (%)	175 (44.87)	9 (47.37)	6 (66.67)*
Bacteremia, n (%)	184 (47.18)	11 (57.89)	5 (55.56)
<i>K. pneumoniae</i> abscess, n (%)	329 (84.36)	17 (89.47)	9 (100.00)
<i>E. coli</i> abscess, n (%)	30 (7.69)	2 (10.53)	0 (0.00)
Anaerobic abscess, n (%)	11 (2.82)	1 (5.26)	0 (0.00)
Cough, n (%)	14 (3.59)	0 (0.00)	3 (33.33)
Dyspnea, n (%)	9 (2.31)	0 (0.00)	3 (33.33)
Shock, n (%)	47 (12.05)	1 (5.26)	3 (33.33)
Respiratory failure, n (%)	28 (7.18)	1 (5.26)	3 (33.33)
Mortality, n (%)	24 (6.15)	0 (0.00)	3 (33.33)

\*Significant difference between Groups B and C,  $p < 0.05$ .

56 years (range, 21–87). Eight patients were admitted through the emergency department (ED) and 1 (patient 9) through the outpatient department of the institution. Their clinical characteristics, including age, gender, clinical manifestations, imaging and non-imaging examination results, therapeutic modalities and prognoses, are summarized in Table 2. Seven of the 9 patients were diabetic, and fever occurred in 5 patients, whilst respiratory symptoms such as dyspnea and cough occurred in 6 patients, and abdominal pain and tenderness in 3 patients. Chest auscultation revealed a crackle over the lower lung fields in 5 patients, and clear breathing sounds in the remainder. Arterial blood gas test was performed in 4 patients, and PaO<sub>2</sub> without oxygen supplementation was in the range of 73.4–92.5 mmHg. The mean duration of patient symptoms prior to the diagnosis of SPE was 6 days (range, 1–13). The average patient hospital stay was 30 days, and ranged from 13 to 66 days. Endophthalmitis coexisted in 3 patients, meningitis in 1 patient, and necrotizing fasciitis in 2 patients.

### Microbiology

Microbiological studies indicated that *Klebsiella pneumoniae* was the responsible pathogen in all 9 patients. The pathogen responsible for patient conditions was isolated from the liver abscess of 5 patients, and from the blood of 5 patients. Other sources of positive culture findings included vitreous fluid (2 patients), cerebrospinal fluid (1 patient), and sputum (3 patients). The sputum culture from patients 4 and 5 also yielded *Pseudomonas aeruginosa* and/or *Acinetobacter baumannii*, although these results were obtained 7 days and 56 days subsequent to admission for both patients, respectively. Patient 4 received the serum cryptococcal antigen test, and sputum *Mycobacterium tuberculosis* was cultured from patient 8, and both showed negative results.

### Imaging studies

One hundred and sixteen patients who were not diagnosed with septic pulmonary embolism had abnormal CXR findings, including pleural effusion (70), non-nodular alveolar infiltration (46), and non-nodular interstitial infiltration (10). However, septic pulmonary embolism was excluded according to a chest CT scan in only 5 of the 116 patients.

Abnormalities of the CXR were noted for all 9 patients upon arrival at our medical institution, and demonstrated ill-defined round densities in peripheral portions of both lobes of the lung. Cavitation of the opacities located within the lung was apparent for 1 patient, and unilateral pleural effusion for 1 patient.

Pulmonary nodules could be identified in all 9 patients, whether through chest CT or abdominal CT including the lower lung fields. The features of septic embolism of the 4 patients who received chest CT included multiple peripheral nodules ( $n=4$ ), cavitations ( $n=2$ ), and feeding vessel sign ( $n=2$ ). Lower lung field wedge-shaped peripheral pulmonary infiltration was found throughout the abdominal CT including the lower lung fields in 1 patient. Three patients died due to sepsis, in which the infiltration seen on the chest film progressed. One of the 3 patients received a serum test for cryptococcal antigen and a sputum *Mycobacterium tuberculosis* culture was carried out for another, both showing negative results.

### Detection of liver abscess

Liver abscess was detected in 4 patients who had experienced neither abdominal pain nor fever, 1 of whom experienced acute blurred vision due to endophthalmitis (patient 3), 1 with a suspected metastatic neoplasm according to the symptom of weight loss and the CXR interpretation (patient 4), 1 featuring malaise and then shock which followed soon thereafter (patient 5), and 1 featuring coma due to meningitis (patient 8). Four patients (patients 4, 5, 6, 8) were initially suspected of having pulmonary infection or neoplasm rather than an underlying liver abscess. Among these patients, liver abscess was detected after a chest CT including the upper abdomen for evaluation of lung opacities in patients 4, 5 and 6, and after abdominal ultrasonography for evaluation of sepsis in patient 8. Abdominal ultrasonography was used for all 9 patients to detect the presence of liver abscess without difficulty, whilst 7 patients also received an abdominal CT including the lower lung fields.

### Treatment programs and prognoses

All 9 patients were administered 2<sup>nd</sup>- or 3<sup>rd</sup>-generation cephalosporin or carbapenem with/without aminoglycosides and/or metronidazole. Two patients received percutaneous “pigtail” drainage for their liver abscess. No patient developed empyema or revealed any evidence of massive hemoptysis. Three patients remained in acute respiratory failure on the 1<sup>st</sup> day of hospitalization, requiring ventilator support, and all of them subsequently died due to acute respiratory distress syndrome and/or septic shock. The remaining 6 patients in our study group survived without any further complication arising during their hospital course, and follow-up CXR demonstrated significant improvement following antimicrobial treatment. We did not observe any identifiable long-term complications resulting from SPE in any of our patients who survived.

**Table 2.** Clinical characteristics and diagnostic modalities of 9 patients with liver abscess and septic pulmonary embolism

No./sex/ age (yr)	Symptoms	Symptom appearance to diagnosis of SPE	CXR	WBC (cells/ mm <sup>3</sup> )	Alk-P (U/L)	CRP (mg/dL)	Microbiologic studies conducted	Treatment	Comorbidity	Other coexisting metastatic foci	Complications arising	Outcome
1/M/70	Fever, dyspnea, abdominal pain	7 d	Ill-defined peripheral densities, cavities	9,800	118	22.2	Liver abscess: K.P Blood: NG	Cefuroxime, metronidazole	Type 2 DM	-	-	Survival
2/M/43	Fever, cough, blurred vision	13 d	Ill-defined peripheral densities, pleural effusion	14,700	328	11.2	Liver abscess: NA VF: K.P Sputum: NG Blood: K.P	Ceftriaxone	-	Endophthalmitis	-	Survival
3/M/79	Low back pain, blurred vision	10 d	Ill-defined peripheral densities	8,830	209	14.3	Liver abscess: K.P VF: K.P Blood: K.P	Ceftazidime, liver abscess drainage, vitrectomy	Type 2 DM	Endophthalmitis	-	Survival
4/F/59	Dyspnea, malaise, weight loss	2 d	Ill-defined peripheral densities	6,500	99	33.1	Liver abscess: NA Sputum: K.P,A,B Blood: NG	Ceftriaxone, amikin, ventilator	Type 2 DM, HTN	-	ARDS, septic shock	Death
5/M/87	Weakness, cough	1 d	Ill-defined peripheral densities	22,000	76	22.6	Liver abscess: NA Sputum: K.P,A,B, P,A Blood: K.P	Tienam, ventilator	-	-	Respiratory failure, septic shock	Death
6/F/21	Vulvar pain, fever, dyspnea	7 d	Ill-defined peripheral densities	9,700	118	27.23	Liver abscess: NA Abdominal wall pus: K.P Blood: NG	Floximef, fasciotomy	Type 2 DM	Necrotizing fasciitis, abdominal wall	-	Survival
7/M/52	Fever, cough, blurred vision, abdominal pain	7 d	Ill-defined peripheral densities	16,100	NA	19.87	Liver abscess: K.P VF: NG Blood: NG	Ceftriaxone, vitrectomy	Type 2 DM, HTN	Endophthalmitis	-	Survival
8/M/44	Consciousness loss	1 d	Ill-defined peripheral densities	8,500	173	26.89	Liver abscess: K.P Sputum: K.P Leg pus: K.P CSF: K.P Blood: K.P	Ceftriaxone, metronidazole, fasciotomy, ventilator	Type 2 DM	Meningitis, necrotizing fasciitis, legs	Respiratory failure, septic shock	Death
9/M/47	Abdominal pain, fever	3 d	Ill-defined peripheral densities	18,600	309	33.5	Liver abscess: K.P Blood: K.P	Ceftriaxone, liver abscess drainage	Type 2 DM	-	-	Survival

A.B = *Acinetobacter baumannii*; Alk-P = initial alkaline phosphatase level; ARDS = acute respiratory distress syndrome; CRP = C-reactive protein level; CSF = cerebrospinal fluid; DM = diabetes mellitus; HTN = hypertension; K.P = *Klebsiella pneumoniae*; NA = no access; NG = no growth; PA = *Pseudomonas aeruginosa*; VF = vitreous fluid; WBC = initial white blood cell count.

## Discussion

*Klebsiella pneumoniae* was the most common pathogen associated with liver abscess, either with or without septic metastases (Table 1). Microbiological studies yielded *K. pneumoniae* as the responsible pathogen in all 9 patients with SPE. The sputum cultures from patients 4 and 5 also yielded *Pseudomonas aeruginosa* and/or *Acinetobacter baumannii*, which implied the presence of nosocomial and ventilator-associated infection. However, bacteremia only occurred in 5 of 9 SPE patients, which may have been due to previous antibiotic use at another hospital in 4 of 9 patients.

Primary *K. pneumoniae*-associated liver abscess is a prevalent infectious complication amongst Taiwanese diabetic patients without other intra-abdominal infection, whilst metastatic infection is a characteristic feature of *K. pneumoniae*-associated liver abscess for Taiwanese diabetic patients.<sup>1-3</sup> The classification of the septic metastatic lesions that arose in the liver abscess patients in this study included endophthalmitis (16), empyema (2), SPE (9), meningitis (3), osteomyelitis (1), psoas muscle abscess (2), chest wall abscess (1), and necrotizing fasciitis (2), which were the same as those observed in previous studies.<sup>1,3</sup> Of 28 patients with septic metastases, 15 (53.5%) had diabetes mellitus, and 26 (92.9%) were confirmed to be infected with *K. pneumoniae*. Three of these 28 patients developed the complication of SPE and died. A rather poor outcome was experienced by patients with respiratory complications who developed liver abscess with septic metastases.

We found that fever (85.2%) and abdominal pain (39.7%) were the 2 most common presenting symptoms for liver abscess, which was compatible with previous studies.<sup>3,8,9</sup> Since abdominal ultrasonography is widely used for evaluating patients with fever and acute abdominal pain, the determination of a diagnosis of liver abscess is, generally, not difficult when assisted by abdominal ultrasonography. It was interesting to find that 4 patients from our study had neither abdominal pain nor fever upon presentation and simply featured dyspnea, acute blurred vision, weakness, or consciousness loss, such that the presence of liver abscess was not included in the differential diagnosis performed by the emergency physician upon patient arrival at the institution. For these 4 patients, the clinical presentations were endophthalmitis, nonspecific weakness, and meningitis. The multiple ill-defined peripheral densities discovered after CXR in patient 4 were initially suspected of being examples of metastatic neoplasm, whilst the presence of liver abscess was detected incidentally using chest CT including the upper abdomen for the purposes of malignancy evaluation. The presence of

liver abscess should always be excluded from the differential diagnosis for diabetic patients presenting with dyspnea, acute blurred vision, sleepiness, or malaise, even for those without abdominal pain or fever.

Our study demonstrates that prompt recognition of SPE is important, as the pulmonary lesions may be 1 of the first manifestations of serious underlying infection. In the setting of bacterial pneumonia, sputum microbiologic examination may only provide a sensitivity of about 50%.<sup>10</sup> Imaging studies often play an additional important role in the diagnosis of infection at a variety of sites. Although bacterial culture of the liver abscess was not obtained for 4 patients, pulmonary nodules could be identified in all 9 patients, whether through chest CT or abdominal CT including the lower lung fields. Septic pulmonary embolism can be diagnosed based on a bacterial culture of the metastatic sites (vitreous fluid, sputum, or abdominal wall pus) and imaging studies of lung and liver. A physician will recognize the presence of SPE if typical characteristic radiographic features of such a condition are observed, particularly those revealed by CT, although it is possible that SPE may be associated with a broader spectrum of radiographic findings than simply lung nodules.<sup>4</sup> CXR findings for SPE include the presence on radiographic films of multiple ill-defined round or wedge-shaped densities located peripherally within the lung and featuring various degrees of cavitation, as was the case for all the patients involved in our study. Alternatively, such a condition may feature the presence of nonspecific or equivocal alveolar infiltrations.<sup>11</sup> The appearance of small scattered lung parenchymal densities on the CXR image may suggest the presence of only mild bronchopneumonia, whereas subsequent CXRs can demonstrate the evolution of scattered areas of increased radiographic density, which often progress to abscess formation.<sup>5</sup>

In patients with SPE who do not have typical CXR findings, CT may demonstrate characteristic findings including the presence of scattered, well-defined parenchymal nodules located within the lungs peripherally, in various stages of cavitation, with definable blood vessels feeding the nodules and heterogeneous, subpleural, wedge-shaped densities seen within the lungs.<sup>12</sup> Chest CT is the most valuable radiologic modality when SPE is suspected. Kuhlman et al demonstrated that the CT features of septic pulmonary embolism included the presence of multiple peripheral nodules (83%), wedge-shaped peripheral lesions (50%), cavitation of nodules (50%), and feeding vessel sign (67%).<sup>13</sup> Iwasaki et al also concluded that the CT findings of subpleural peripheral nodules and wedge-shaped peripheral lesions < 30 mm in diameter are often found in

patients with septic pulmonary embolism.<sup>14</sup> All our 9 patients featured peripheral nodules and a potential embolic source, allowing us to consider septic pulmonary embolism. However, the differential diagnoses of multiple pulmonary nodules include tuberculosis, fungal infection and tumors. While resolution of lung infiltrates after appropriate antimicrobial therapy is a clue that septic pulmonary embolism has been correctly diagnosed, investigations to exclude other potential causes of the lung lesions should also be arranged. Three patients died due to sepsis, in which the infiltration seen on the chest film progressed. Only 1 of the 3 patients received a serum test for cryptococcal antigen to exclude *Cryptococcus* infection, and *Mycobacterium tuberculosis* was cultured for 1 patient, both of which showed negative results. The investigation of lung nodules seemed inadequate. However, according to the clinical presentation of sepsis, and results of imaging and microbiologic studies, SPE was suggested.

The case definition of SPE in our analysis mainly relied on the CT features of SPE. Cook et al created their definition of SPE according to those of other authors and their own experience.<sup>4</sup> However, they did not clearly demonstrate how to achieve the criteria for exclusion of other potential explanations for lung infiltrates. Our 9 cases did not receive extensive examinations to exclude other explanations for lung infiltrations except 2—1 was serum cryptococcal antigen and the other was a sputum *Mycobacterium tuberculosis* culture, both showing negative results. No patient received sputum cytology examination. For the above reason, we did not add any exclusion criteria to this retrospective analysis. We thus recommend that sputum cultures for *Mycobacterium tuberculosis* and fungus, sputum cytology, and a bacterial culture of the embolic source should be obtained in patients with CT findings of peripheral lung nodules.

There were 4 main limitations to this study. First, the sample size was small. This is probably a consequence of the rarity of liver abscess patients with SPE, and some cases may progress rapidly to death before an accurate diagnosis of liver abscess with the complication of SPE can be made. Second, 4 patients were referred from local hospitals and antibiotics had been prescribed there, which may have resulted in a low incidence of bacteremia in this study. Greater confirmation of the incidence of bacteremia might have been achieved if the original blood culture from the local hospitals had been obtained. Third, only cases with typical characteristic radiographic features were enrolled in this study. Although the lung window of an abdominal CT scan including the lower lung fields may show septic embolism near the diaphragm, it is an inappropriate imaging

study to identify SPE. In SPE patients with radiographic findings other than multiple ill-defined peripheral round densities, the CXR may be interpreted as pneumonia and the incidence of SPE may be underestimated if a chest CT scan is not carried out. Fourth, 2 sets of blood culture were not routinely performed for all patients, which normally were taken before antibiotic usage and liver abscess aspiration for pathogenic confirmation. This may have led to incorrect data analysis of risk factor identification.

The present study has shown that diabetic patients with liver abscess may present with SPE during ED visits. On the other hand, chest CT scans can be arranged in diabetic patients with liver abscess who have abnormal CXR findings showing multiple ill-defined peripheral round densities in order to detect SPE, which has a relatively poor outcome in liver abscess patients with septic metastases.

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