

Original article

Factors related to complications and mortality in pyogenic liver abscesses

A. Alexopoulou¹, H. Dimopoulou¹, A. Soultati¹, G. Panetsos², S. P. Dourakis¹

SUMMARY

Background: Pyogenic liver abscess (PLA) is the most common type of visceral abscess. We recorded multiple variables of the disease and assessed those associated with disease severity and mortality. **Methods:** The medical records of 33 patients were reviewed. **Results:** Source of infection was identified in 27.8% of cases. The majority of PLA were located in the right lobe. The most common isolated microorganism was *Escherichia coli*. Complications including basilar infiltrates, pleural effusions, pylephlebitis and septic shock developed in 12 cases (36.4%). Factors associated with complications on univariate analysis were the large size of the abscess ($p < 0.05$, OD 1.8, 95% CI 1.7-2.1), a urea level more than 55 mg/dl at presentation ($p < 0.05$, OD 1.7, 95% CI 1.5-1.9) and delay in diagnosis ($p < 0.05$, OD 1.3, 95% CI 0.9-1.6). Two deaths (6%) from sepsis were recorded. Factors associated with mortality on univariate analysis were bilirubin > 2 mg/dl ($p < 0.05$, OD 1.0, 95% CI 0.9-1.1), antibiotics alone without prompt drainage ($p < 0.05$, OD 1.3, 95% CI 1.1-1.5), bilobar involvement ($p < 0.05$, OD 1.3, 95% CI 1.1-1.5) and occurrence of complications ($p = 0.05$, OD 1.0, 95% CI 0.9-1.1). **Conclusions:** Our results suggest that the prognosis in PLA is related to severity of medical condition and early diagnosis and management. PLA still remains a clinical entity with high morbidity and mortality.

Key words: pyogenic liver abscess; retrospective study; risk factors; prognosis; complications

INTRODUCTION

PLA has an annual incidence of 2-35 cases per 100,000 admissions^{1,2} and it is more common in men than in women.^{1,3,4}

Historically, this entity has been associated with high mortality rates³ which have changed the last decades due to the advent of modern diagnostic techniques i.e. liver ultrasonography (US) and computed tomography (CT) scanning. These techniques allowed precise localization and the minimal invasive image-guided percutaneous aspiration and drainage that have widely replaced the open surgical procedures.⁴ These relatively new therapeutic options have reduced mortality to 2-12%.^{3,5} Risk factors for the development of PLA included diabetes, hepatobiliary and pancreatic malignancies and immunosuppression but in the majority of PLA no risk factor is demonstrated.^{1,3,4,6}

Our own experience prompted a retrospective review of 33 cases with PLA over a 11-year period in a single tertiary Center in Greece. The aims of this study were to describe the parameters related to the development of PLA and analyse the risk factors related to complications and mortality.

PATIENTS AND METHODS

Data collection

The medical records of 33 patients diagnosed with PLA in Hippokratation University Hospital of Athens between January 1998 and December 2008 were retrospectively reviewed. The patients were enrolled by an electronic systematic search of the patients' records for diagnostic codes. The study was approved by the Institutional Review Board. Diagnosis of PLA was based upon the co-evaluation of a) yield of bacterial pathogens from blood or liver abscess cultures and b) identification of one or more discrete abscess cavities in the

¹2nd Department of Medicine, Medical School, University of Athens, Hippokratation Hospital, Athens, Greece, ²Department of Surgery, Hippokratation Hospital, Athens, Greece

Author for correspondence:

Dr Alexandra Alexopoulou, 40 Konstantinoupoleos St, 16342 Hilioupolis, Athens, Greece. Email alexopou@ath.forthnet.gr, Tel +30 210 7774742, Fax +30 210 7706871

liver by computed tomography (CT) scan with contrast enhancement. Medical records were scrutinized for demographic characteristics, underlying medical conditions, initial clinical manifestations, laboratory findings, imaging and microbial findings, treatment and overall morbidity and mortality.

Clinical, imaging, laboratory and microbiological parameters

Demographic and clinical characteristics comprised age, sex, underlying medical conditions (diabetes mellitus, biliary disorders, hemodialysis, liver cirrhosis, malignancy, immunosuppression, cavities from old calcified echinococcus cysts, simple benign liver cysts), symptoms and signs at presentation and origin of the abscess. Patients receiving empiric therapy with antibiotics prior to admission were also recorded. The origin of the abscess was based upon imaging studies. When a monomicrobial PLA due to streptococcal or staphylococcal species was documented a trans-oesophageal heart US was performed to exclude endocarditis. The origin of the abscess was defined as cryptogenic when no causative infection lesion was demonstrated. The liver abscess were characterised according to the following parameters: size, location, number, gas forming and loculation of subcollections. All the patients had a chest and abdominal radiography on admission. Blood cultures were obtained by all the patients on admission.

Microbiological parameters included Gram stain and growth of bacteria in the blood culture or the culture of the abscess material obtained by aspiration. Bacteremia, polymicrobial infection and anaerobic infection were recorded. The abscess material was obtained by US or CT guided percutaneous needle aspiration (NA) or catheter drainage (CD). No surgical procedure was performed. Serology for amoeba histolytica was available in all patients and if the test was negative aspiration was performed if needed. Bacterial cultures by aerobic and anaerobic diagnostic methods and tests for antimicrobial susceptibility were performed. Negative blood culture bottles were incubated for seven days before being reported negative. Blood culture isolates were identified using standard microbiological procedure and further confirmation was done using commercially available API strips.⁷ Antibiotic sensitivities of all isolates except non enterobacteriaceae were carried out using Kirby Bauer method.⁸

Complications were considered as pulmonary i.e. pleural effusion, pulmonary basilar infiltrate, abdominal i.e. portal vein thrombosis and the development of sepsis. Factors related to complications and mortality were analysed.

Laboratory parameters included erythrocyte sedimentation rate (ESR), white blood cell count (WBC), C-reactive protein (CRP), platelet count, serum urea, aspartate aminotransferase (AST), alkaline phosphatase (ALP), serum bilirubin and serum albumin.

All patients were treated with parenteral antibiotics for at least 2 weeks followed by oral antibiotics to complete 6 weeks of treatment. The antimicrobial treatment was empiric initially pending culture and following culture results, it was tailored according to the available susceptibility tests. NA or CD aspiration of the abscess material was also used for the majority of the lesions. Repeat NA procedures were recorded. Response to treatment was evaluated in each patient by clinical parameters such as temperature, white blood cell count, C-reactive protein and a series of follow-up US or CT scans of the liver until resolution or minimalization of the cavity lesion. Patients with abscesses that were slow to resolve on follow-up imaging often required longer courses of therapy and hospitalization. Case fatality was defined as death during hospitalization.

Statistical analysis

Continuous data were summarized as means with standard deviation (SD) and categorical data as percentages. Comparisons were considered significantly different for p values < 0.05 . Statistical significant factors of mortality were identified by univariate analysis. The prognostic factors used for analysis of mortality were the following: demographic characteristics (age, sex), laboratory findings (serum urea and albumin, white cell count, total bilirubin, ESR, CRP, platelet count, AST and ALP), radiologic findings (size, number and location of the abscess, multiloculation, gas-forming), microbiological features (anaerobes, polymicrobial infection), origin (biliary or not), underlying malignancy, delay in diagnosis and presence of complications. The prognostic factors used for analysis of complications were all the above apart from the last one. Odds ratio (OR) and their 95% confidence intervals (CI) were calculated. All statistical analyses were conducted with the software SPSS 17.0 for Windows.

RESULTS

Clinical parameters and aetiology

The study group included 22 men and 11 women, of mean age 61 years ranging from 23 to 85 years. Prior to admission 18 (54.5%) patients received empiric antibiotic therapy by general practitioners. Benign or malignant disorders of liver, pancreas and biliary tract accounted for 15 (45.4%) patients. Benign disorders of the liver and biliary

tract accounted for 9 (27.2%) cases (cholangitis n=1, cholepeptic anastomosis n=2, liver cirrhosis n=1, liver transplantation n=1, old calcified echinococcal cyst n=3, multiple benign liver cysts n=1) while malignancies of the liver, pancreas and biliary tract accounted for 6 (18.2%) cases (hepatocellular carcinoma n=1, cholangiocarcinoma n=2, liver metastases from colorectal cancer n=1, liver metastases from stomach cancer n=1, pancreatic cancer n=1) (Table 1). Diabetes mellitus accounted for 9.1% of cases. Demographic characteristics and clinical data on presentation are also shown in Table 1. The most common initial clinical manifestations were fever (97%) and abdominal pain (75.7%). The origin of infection was not identified in the majority of the patients (72.7%).

Imaging and laboratory findings

The majority (69.7%) of liver abscess involved the right lobe, they were 5-9 cm in size (63.6%) and solitary (75.7%) (Table 2). Multiple abscesses were observed in 24.2% of patients. The presence of elevated hemidiaphragm (42.4%), pleural effusion (18.2%) and basilar infiltrate (6%) in chest radiography was also noted. PLA was

accompanied by pylephlebitis in 1 patient. Gas forming PLA were observed in 4 patients (12.1%) and loculated subcollections in the abscess in 3 (9%). All the patients had elevated CRP and the majority had elevated WBC and ESR. Elevated AST, ALP, total bilirubin and abnormally low serum albumin were observed in 39.4%, 45.4%, 24.2% and 45.4% of patients respectively (Table 2).

Microbiological findings

A microorganism was isolated in blood culture in 27.3% (9/33 patients) and the frequency of positive culture in abscess material was 64.3% (18/28 patients) in whom abscess cultures were obtained (Table 3). *Escherichia coli* was the most commonly isolated gram-negative micro-organism. *Streptococcus spp* was the most commonly isolated gram positive micro-organism. Anaerobic isolates from blood or abscess culture were found in only 1 patient. Polymicrobial infection was involved in 15% (5/33 patients). Considering the microbiological findings in relation with the origin of the PLA, no predilection of any specific micro-organism with a biliary or cryptogenic origin was observed.

Table 1. Demographic data, underlying diseases, origin of the abscesses, and presenting symptoms and signs

Gender, male/female	22(67%) / 11(23%) ((33%) (35%))
Age, mean \pm SD (years)	60.9 \pm 17.1
<i>Underlying disease</i>	
• Diabetes mellitus	3 (9.1 %)
• Benign biliary disorders (cholepeptic anastomosis, cholangitis)	3 (12.1%)
• Hemodialysis	1 (3%)
• Liver cirrhosis	1 (3%)
• Malignancy (pancreatic or hepatobiliary origin)	6 (18.2%)
• Immunosuppression (liver transplantation, rheumatoid arthritis under corticosteroids, chronic granulomatous disease)	3 (9.1 %)
• Old calcified echinococcus cyst	3 (9.1 %)
• Benign liver cysts	1 (3%)
Patients who received antibiotics empirically prior to admission	18 (54.5%)
<i>Symptoms</i>	
• Fever	33 (96.7%)
• Abdominal pain	25 (75.7%)
<i>Signs</i>	
• Low systolic blood pressure (<100 mm Hg)	3 (9.1%)
• High pulse rate (>100 min)	5 (15.1%)
• Jaundice	4 (12.1%)
• Ascites	1 (3%)
<i>Origin of abscess</i>	
• Biliary origin†	8 (24.2%)
• Cryptogenic origin	24 (72.7%)
• Transcatheter embolisation for hepatocellular carcinoma	1 (3%)

†Biliary origin of liver abscess included suppurative cholangitis (n=1), cholepeptic anastomoses without malignancy (n=2), cholepeptic anastomoses because of hepatobiliary or pancreatic malignancies (n=4), and biliary stenting because of biliary malignancy (n=2)

Table 2. Characteristics of the liver abscesses regarding location, size, number, laboratory and microbiological findings and complications.

Characteristic	N (%)
• Location of abscess	
• Right lobe	23 (69.7%)
• Left lobe	6 (18.2%)
• Bilobar involvement	6 (18.2%)
<i>Abscess size</i>	
• <5 cm	7 (21.2%)
• 5-9 cm	20 (63.6%)
• ≥10 cm	6 (15%)
Multi-loculated	3 (9%)
<i>Number of abscess</i>	
• Solitary	25 (75.7%)
• Multiple	8 (24.2%)
Gas forming abscess	4 (12.1%)
Septic shock	3 (9%)
Pylephlebitis	1 (3%)
<i>Chest radiography findings</i>	
• Elevated right hemidiaphragm	14 (42.4%)
• Pleural effusion	6 (18.2%)
• Basilar infiltrate	2 (6%)
<i>Laboratory studies</i>	
• ESR > 100 mm/h	20 (60.6%)
• C-reactive protein > 5 mg/dl	33 (100%)
• Leukocytosis > 11 x 10 ⁹ /l	27 (81.8%)
• Thrombocytopenia < 150 x 10 ⁹ /l	3 (9%)
• AST > 40 IU/l	13 (39.4%)
• Urea > 55 mg/dl	7 (21.2%)
• Elevated ALP (126 IU/l)	15 (45.4%)
• Serum total bilirubin > 2 mg/dl	8 (24.2%)
• Serum albumin < 35 g/l	15 (45.4%)
<i>Microbiological studies</i>	
• Bacteremia	9 (27.3%)
• Polymicrobial infection	5 (15.1%)
• Anaerobic infection	1 (3%)

Treatment

Initial empirical antibiotics including penicillins, cephalosporins, aminoglycosides, quinolones and metronidazole were administered to all patients. The initial antibiotics had changed when appropriate according to the susceptibility of the micro-organism when available. Apart from antibiotics drainage was performed during the first 24 hours in 9 patients using image-guided NA method and in 16 patients using the CD method. In one patient both the above methods were used. Seven patients were treated with antibiotics, alone without any drainage. Five of them had multiple abscesses less than 3 cm in diameter. No patient underwent surgery.

Table 3. Microorganisms and source of isolation

Bacteria	Blood [9 (27.3%) patients]	Abscess [18 (64.3%) patients]
Gram negative aerobes		
• <i>Escherichia coli</i>	3	5
• <i>Klebsiella pneumonia</i>		1
• <i>Klebsiella oxytoca</i>	1	
• <i>Proteus spp</i>		2
• <i>Enterobacter spp</i>	1	2
• <i>Pseudomonas spp</i>	1	1
• Unidentified Gram (-) bacilli		2
Gram positive aerobes		
• <i>Enterococci spp</i>	2	2
• <i>Staphylococci spp</i>	1	1
• <i>Streptococci spp</i>	3	3
• Unidentified Gram (+) bacilli		2
Anaerobes		
• <i>Bacteroides spp</i>		1
Total isolates	12	22

More than one microorganism were isolated in 5 patients

1st patient: *E. cloacae*, *P. aeruginosa*, *P. mirabilis*

2nd patient: *E. cloacae*, *P. mirabilis*

3rd patient: *Bacteroides spp*, *Streptococcus spp*

4th patient: *K. pneumoniae*, *Enterococcus spp*

5th patient: *E. coli*, *S. intermedius*

Morbidity and mortality

Complications including basilar infiltrates, pleural effusions, pylephlebitis and septic shock developed in 12 cases (36.4%). Factors associated with complications on univariate analysis were the large size of the abscess ($p < 0.05$, OD 1.8, 95% CI 1.7-2.1), a urea level more than 55 mg/dl at presentation ($p < 0.05$, OD 1.7, 95% CI 1.5-1.9) and delay in diagnosis ($p < 0.05$, OD 1.3, 95% CI 0.9-1.6). The variables age, sex, source of infection, location of the abscess, type of treatment or other laboratory findings were not related to the development of complications.

Two deaths were recorded (6%). The first was recorded in a 65 year-old male who had two large abscesses in both liver lobes. The diagnosis and drainage were delayed because liver malignancy was initially suspected. He died from sepsis. The second patient was a 70-year old male suffering from stomach cancer with liver metastases. He had multiple abscesses involving both lobes of the liver and he also died from sepsis. The diagnosis of liver abscesses was delayed because of the underlying disease. The rest of the patients (94%) were discharged after a mean of 25.9 ± 11.8 days of hospitalisation. No variable was related to the duration of hospitalization.

Factors associated with mortality on univariate analysis were bilirubin > 2 mg/dl ($p < 0.05$, OD 1.0, 95% CI 0.9-1.1), antibiotics alone without prompt drainage ($p < 0.05$, OD 1.3, 95% CI 1.1-1.5), bilobar involvement ($p < 0.05$, OD 1.3, 95% CI 1.1-1.5) and occurrence of complications ($p = 0.05$, OD 1.0, 95% CI 0.9-1.1). No other variable was associated with mortality.

DISCUSSION

The data analysed confirmed the generalized tendency of PLA to male gender preponderance and old age.¹⁻⁴ We did not find any association between age or gender and mortality unlike other studies showing a worse outcome for older patients and for female gender.^{1-4,9} An underlying disease or abnormality, systemic or localised to the liver, predisposing to abscess formation was recognised in approximately half of the patients. We should point out that diabetes as a specific predisposing factor accounted for just a low rate of the cases compared to that described in the literature.^{4,12} In addition, no case of gas forming PLA was observed in the 3 patients with diabetes unlike to the results of previous studies. Echinococcal cysts treated in the past with aspiration and alcohol ingestion accounted for a few cases. A contamination of echinococcal cysts resulting in the formation of liver abscess has been described in the literature. However in our patients only the old cavity was present and the infection was inactive since no parasites were detected in the fluid material.

The most frequent clinical findings were fever and abdominal pain accounting for similar rates described in the literature.^{1-4,12} Regarding the etiology, no known source of infection was identified in the majority of cases. Unlike to the findings in other studies¹² the presence of diabetes (which was present at a low rate in our study) was not related to the cryptogenic etiology in our series. Hepatobiliary diseases such as biliary tract obstruction due to malignancy or gallstones, accounted for 40-60% in the literature.^{1,8,10,11} In our series, initial approach by a liver ultrasonography and a CT scan of the abdomen was not always ensued by MRCP or ERCP for the thorough investigation of the biliary tract. Even though underlying diseases of the liver such as pre-existed cavities (old echinococcal or simple cysts), hepatobiliary malignancies and old cholepeptic anastomoses with or without malignancies accounted for a considerable number of our cases, biliary tree was not always the obvious origin of infection. Some authors recommend a thorough search of the biliary tree in order to identify a possible focus of infection.^{12,12} Hence biliary tract disease as the cause of PLA could have escaped from diagnosis in some of our cases.

Frequent laboratory findings in our series were elevated C-reactive protein and ESR, leucocytosis, a rise in ALP and hypoalbuminemia. In the imaging studies, solitary PLA usually located in the right lobe of the liver was the predominant finding consistent to that observed in the literature.^{4,13} APACHE score which was considered a valuable parameter in previous studies¹⁴ was not determined since we studied the patients data retrospectively and some of the parameters of the above score were not recorded.

The most frequent complications were the pulmonary ones including pleural effusions and basilar infiltrates shown in one fifth of patients. Only one case developed pylephlebitis as an abdominal complication. Large size of the abscess was the sole factor predicting the development of complications. As far as mortality is concerned, the two deaths occurred in patients with hyperbilirubinaemia, bilobar involvement and delay in diagnosis. It seems therefore that prognosis of PLA is rather related to various factors as the condition of the patient, the features of the abscess itself and the type of management by the physician. Mortality rate accounted for 6% which is similar to that observed in the literature.^{3,8} Despite the modern imaging techniques used for diagnosis and management, PLA is still an entity with considerable mortality.

A positive result from both blood culture and PLA aspiration material was obtained from a relatively low proportion of patients. The administration of antibiotics prior to admission may be implicated in the relatively low rates of isolation of bacteria in the current study. Among the positive cultures mono-microbial ones were the most frequent. Gram negative bacteria were the most frequent isolates and within these germs *E.coli* was the most prevalent pathogen. The above isolated organism has previously been described by other investigators.^{4,15} Among the Gram positive bacteria, *Streptococcus spp* were the predominant pathogen. The parameters of bacteremia, type of bacterium (Gram positive or negative) and poly-microbial infections were not related to a worse outcome in our series unlike that previously described.⁴ No multi-resistant strains were isolated in blood or PLA aspiration material cultures.

Antibiotic treatment was administered intravenously for at least 2 weeks followed by a long course of antibiotics orally. The majority of patients underwent a catheter or needle aspiration drainage of the abscess under ultrasonography guidance. No advantage of either method regarding complications, days of hospitalization, or mortality was identified. NA seemed to be as effective as CD as previously reported.^{17,19} Ultrasonography seems to be a valuable diagnostic and therapeutic tool for the management of liver

abscess since it allows visualisation of the liver and biliary tree, needle aspiration and catheter drainage.

In conclusion, PLA remain a life-threatening disease with considerable rates of morbidity and mortality. Prompt diagnosis and combined treatment with both antibiotics and drainage remain the milestones of management. Extended disease, poor condition of the patient and delay in diagnosis and consequently treatment are associated with the worst outcome.

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