Hepatic Abscesses After Liver Transplant: 1997–2008

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Abstract

Objectives: **Infectious complications (such as liver abscesses) remain one of the major causes of posttransplant morbidity and mortality. Management may be problematic and is often based on experience with hepatic abscess in nontransplant patients. We reviewed our experience with hepatic abscess in liver transplant recipients to assess their presentation, clinical features, treatment, and outcome.**

Materials and Methods: **A retrospective review of all liver transplant in Shiraz transplant center from September 1997 through September 2008 was performed. Hepatic abscess was defined as a parenchymal hepatic lesion consistent with abscess (as described by a radiologist), positive liver or concurrent blood cultures, or both (within 24 hours), and compatible clinical findings.**

Results: **Of 560 liver recipients, we identified 5 patients (23-42 y) who had experienced 7 episodes of hepatic abscess, 30-240 days after transplant. All patients had received liver from deceased donors. Biliary reconstruction was done by duct-to-duct anastomosis in 4 and hepatico-jejunostomy in 1 case. Pretransplant diagnoses included hepatitis B cirrhosis, autoimmune hepatitis (2 cases), Caroli disease, and cryptogenic cirrhosis. Liver aspirates showed *E. coli* in 4 cases, and *Aspergillus* in 1 case. The main predisposing factor was bile-to-duct anastomosis stricture in 3, diabetes mellitus in 2, and hepatic artery thrombosis in 1 of the patients. Two patients died owing to liver and multiorgan failure, despite percutaneous and operative drainage with broad spectrum antibiotics and antifungals.**

Conclusions: **Hepatic abscess, a rare complication after liver transplant, was associated with hepatic artery thrombosis, biliary anastomosis stricture, and diabetes mellitus. Mortality was higher than in patients who had not undergone transplant. Prolonged antibiotic therapy and drainage are required to improve the outcome in these patients.**

Key words: *Posttransplant Complications, Morbidity, Management, Diagnosis, Pyogenic*

Liver transplant is a well-established therapy for end-stage liver disease. In recent years, growing experience has markedly improved patient outcome after orthotopic liver transplant. Consequently, long-term complications arise with increasing frequency (1, 2). In spite of progress made in surgical technique, and antibiotic or immunosuppressive treatment, infectious complications remain one of the major causes of posttransplant morbidity and mortality (3, 4). The development of infection in liver transplant recipients is related to their poor medical condition and the complexity of performing a surgical procedure in a potentially contaminated environment in immuno-suppressed patients. Increase in immunosuppression due to antirejection treatment, steroid-bolus therapy, and the requirement for OKT3, leads to an increase in infection, including pneumonia, cholangitis, and sepsis. These infections may be bacterial, fungal, or viral in nature (5). Sometimes these infections clinically presents as a hepatic abscess.

Previous studies of liver abscess in solid-organ transplant recipients have been limited to isolated case reports and limited descriptions in the published

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medical literature (6-10). Over the past century, the diagnosis and treatment of hepatic abscess has remained a challenge to physicians. Management may be problematic and is often based on experience with hepatic abscess in nontransplant patients. It is necessary to know more about these infections to control and, if possible, prevent them. We reviewed our experience with hepatic abscess in liver transplant recipients to assess their presentation, clinical features, treatment, and outcome.

Patients and Methods

A retrospective review of all liver transplants in Shiraz transplant center, from September 1997 until September 2008 was performed. Patients whose discharge codes included "transplantation" and "liver abscess" were included in the study. Individual medical charts were reviewed, and information included data on patient sex, age, cause, and indication for transplant, interval from transplant to diagnosis, treatment, complications and duration of follow-up, and survival were abstracted in data sheets. The follow-up period ranged from 8 months to 11 years.

Hepatic abscess was defined as a parenchymal hepatic lesion consistent with abscess, as described by imaging studies (ultrasonography or computerized tomography scan with and without intravenous contrast), positive liver aspirate or concurrent blood cultures, or both (within 24 hours), and compatible clinical findings. Cure was defined as resolution of the hepatic lesion on repeat radiographic imaging, with associated clinical improvement, and stable clinical course after antibiotic treatment was discontinued. Alternatively, infection was considered to be associated with death if the patient was undergoing antibiotic treatment when death occurred. We excluded those hypoechoic or hypodense hepatic lesions, which aspirates showed only necrotic tissue or not associated with positive microbiologic cultures.

Statistical analyses and tabulation of data were performed with SPSS statistical analyses SPSS software for Windows (Statistical Product and Service Solutions, version 15.0, SSPS Inc, Chicago, IL, USA).

Results

Of 560 liver recipients, we identified 5 patients who had experienced 7 episodes of hepatic abscess. One case had admitted 2 times due to liver abscess during 1 month before admission (case 2). The mean age of patients was 33 (range, 23-42 years). Timing of presentation was variable with range 30-240 days after transplant (median 60 days). All patients had received liver from deceased donors with cold ischemia time between 8 to 12 hours. Biliary reconstruction was done by duct-to-duct anastomosis in 4 and hepatic-ojejunostomy in 1 case.

Table 1. Laboratory data on presentation with hepatic abscess of liver transplant patients.

Case	WBC	Hemoglobin	INR	Albumin	Total bilirubin	Alkaline phosphatase	AST	ALT
Case 1	4100	11.2	1.4	3.1	12.4	393	116	103
Case 2	12200	10	1.65	2.6	8.6	1420	74	48
Case 3	14900	8.5	1.6	2.8	0.8	518	8	18
Case 4	16900	12.3	1.14	3.1	2.4	393	19	10
Case 5	13000	11.3	2.13	3	4.7	841	74	149

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; WBC, white blood cells.

Immunosuppression at the time of diagnosis included prednisolone and mycophenolate mofetil in all of 5 patients plus cyclosporine in 2 and tacrolimus in 3 patients (Table 2). Pretransplant diagnoses included hepatitis B cirrhosis, autoimmune hepatitis (2 cases), Caroli disease, and cryptogenic cirrhosis. Liver aspirates showed *E. coli* in 4 cases and was unknown in 1 case (Table 2). On physical examination, 80% of our patients had both right upper quadrant abdominal tenderness and fever > 38°C; also 80% of patients had clinical jaundice. One patient presented with pulmonary edema (case 3) and 1 patient (case 4) had bowel obstruction along with liver abscess. Positive past histories in our series were present in case 2 as 2 times of admissions in hospital due to liver abscess and in case 3 as admission in hospital due to peritonitis with Escherichia coli (*E. coli*) together with acute renal failure 3 weeks before admission. Hypoalbuminemia (< 3.5 g/dL) was seen in all patients in our study. International normalized ratio was considered to be prolonged (> 1.21) in 80% of cases (Table 2). The clinical and microbiologic characteristics of our cases are shown in Table 2.

The most common predisposing factor was included bile duct anastomosis stricture in 3 patients, diabetes mellitus in 2 cases (40%). Two (cases 1 and 2) of 3 cases of bile duct stricture were diagnosed 40 days and 60 days after transplant respectively, treated by Roux-en-Y choledochojejunostomy. The other case (case 5) (diagnosed at the time of admission) but the patient died before definite treatment.

Case one developed hepatic artery thrombosis 10 days after transplant, diagnosed with color Doppler

Table 2. Characteristics of recipients who developed hepatic abscess *days.

Case	Presentation	Predisposing factor	Duration *	S vs. M	Calcineurin inhibitor	Liver aspirate culture	Blood culture	Presentation after OLT *	Complications	Death
1	Fever, abdominal pain	HAT, Bile Duct stricture	8	S	Tacrolimus	*Aspergillus*	Negative	40	Rejection	No
2	Fever, abdominal pain	Bile duct stricture, Diabetes mellitus	10	M	Tacrolimus	*E. coli*	Negative	240	Hypokalemia, UTI, ascites	Yes
3	Dyspnea, chills	Heart failure, positive Hx of peritonitis	4	S	Cyclosporine	*E. coli*	Negative	90	Large anterior abdominal wall ameobic collection, UTI, ascites, SBP	No
4	Fever, vomiting, abdominal pain and distension	Bowel obstruction	12	S	Tacrolimus	*E. coli*	Negative	30	Ascites, UTI	No
5	Fever, chills, abdominal pain	Bile duct stricture, diabetes mellitus, portal vein thrombosis	10	M	Cyclosporine	*E. coli*	Negative	60	Uremia, SBP, Wound infection, ascites	Yes

Abbreviations: Hx, history; M, multiple; OLT, orthotopic liver transplant; S, single; SBP, systolic blood pressure; UTI, urinary tract infection.

sonography and confirmed with angiography and thrombolysis by streptokinase was performed for her and due to not responding to therapy, hepatic artery reconstruction by a jump graft from aorta was done after 12 hours. Liver biopsy, which was done during laparotomy in case 5, was in favor of venous outflow obstruction and superimposed ischemic damage.

Solitary abscess was seen in 60% of cases, all located in the right lobe of the liver. Multiple abscesses were noted in the 2 cases. Mean length of hospital stay was 34 days. Duration of follow-up for survivors was an average of 524 days (range 130-1640). Liver abscesses were located in right lobe, except in case 5, who had liver abscess in both lobes.

Patients received an average of 6 weeks of intravenous antibiotic therapy. Once their clinical status improved, treatment was completed outside of the hospital. Afterwards, patients usually continued on an oral program for at least several weeks. Serial, weekly, US imaging was used to assess response to treatment. Four cases were treated by percutaneous catheter drainage, under guide of ultrasonography (US). Case 2 required repeat drainage 3 times, and case 5 needed 2 times, because of displacement or occlusion of the drain or persistent hepatic abscess. Finally, case 2 showed improvement, but case 5 was taken for open drainage. Case 4 was also underwent laparotomy because of concomitant bowel obstruction.

Complications are shown in Table 2. The most common complications were ascites and urinary tract infection, which is diagnosed by growth of 10^5 colony of *E. coli* in urine culture. Case 2 developed hypokalemia and ascites and was treated with medical therapy. Unfortunately, the patient died due to liver failure and massive bleeding. Complications of case 5 consisted of 1- uremia which cause him to undergo hemodialysis 2 times. 2-wound infection with pseudomonas, which was diagnosed by culture. It was sensitive to Amikasin, which was added to medication. 3-secondary bacterial peritonitis (SBP) diagnosed by aspiration of ascites fluid. Case 3 developed a large anterior abdominal wall collection, which was in favor of hematoma in the US. Collection was drained with catheter by US guidance and analysis was in favor of amoebic collection. Culture and characteristic of aspirates were not available, unfortunately. He had previously taken metronidazole, parenterally. Despite great medical treatment, the patient died due to sepsis and multiorgan failure.

Discussion

Liver transplant has evolved as a successful treatment for patients with end-stage liver cirrhosis and acute liver failure. Improvements in immunosuppression, perioperative management, and surgical techniques have allowed survival figures of greater than 90% for 1-year patient survival and 70%-80% for 10 years (5). However, the range of possible postoperative complications is broad, and ranges from minor to severe.

The spectrum of complications includes technical complications, medical complications such as pneumonia and sepsis, and immunologic complications like acute rejection (5). Biliary complications are certainly the most frequent complications after liver transplant (11). Pneumonia is the most frequent source of early postoperative infection, followed by cholangitis and sepsis (12). Bubak and associates reported increased risk of post liver biopsy infectious complications in liver transplant patients who had undergone Roux-en-Y

choledochojejunostomy as part of the transplant operation (13).

Few studies have discussed about abscess after liver transplant. A case of *Candida* (Torulopsis glabrata) liver abscess was reported 8 years after orthotopic liver transplant by Annunziata and associates (10). Tachopoulou, reported 12 cases of liver abscess among liver transplant patients (14). In the other studies, only 2 cases of hepatic abscesses were reported in liver transplant recipients (15, 16). There were 5 cases of liver abscess in our center during an 11-year period. It is possible that there may have been patients originally transplanted at our institution who were diagnosed with hepatic abscess and treated at another facility and, thus, have remained unaccounted. However, in nearly all instances, transplanted patients who develop a complication are transferred here for further management.

Most pyogenic liver abscesses develop within the first 3 months after orthotopic liver transplant (4, 14). In our study, the median time from transplant to liver abscess was 2 months. Most patients in our series presented with fever and abdominal pain, like nonimmunocompromised patients.

Biliary stricture occurs in approximately 6% to 34% of cases, most of them within 3 months of transplant (11, 17). Hepatic abscess in the nontransplant patients is commonly associated with both benign and malignant biliary obstruction. Huang and associates reported that 50% to 60% of the patients with pyogenic abscesses had associated biliary pathology (18). Two (cases 1 and 2) of 3 cases of bile duct stricture were diagnosed 40 days and 2 months after transplant, respectively, and treated by Roux-en-Y choledochojejunostomy. The other case (case 5) diagnosed at the time of admission, but patient died before treatment.

Hepatic artery thrombosis was the most lethal condition associated with hepatic abscess ranging from 3.1% to 7.1% (19). Mean time of presentation of hepatic artery thrombosis in adults was reported 128 days in 1 study (20). In our series, 1 of 5 patients developed hepatic artery thrombosis 12 days after liver transplant. This patient referred due to abdominal pain and in workup, Doppler sonography revealed low flow hepatic artery, and hepatic artery thrombosis was finally confirmed with magnetic resonance angiography.

Clinical presentation of hepatic artery thrombosis is variable. Patients may present with fulminant hepatic necrosis, delayed bile leakage, relapsing bacteremia (21) or may be unsuspected clinically, diagnosed only at the US or autopsy (22). Hepatic artery thrombosis causes ischemic injury to graft, making conditions suitable for hepatobiliary infections (13, 23). Most of the cases of hepatic artery thrombosis usually lead to retransplant (19). Due to dangerous complications, serial imaging studies should be done to evaluate patency of hepatic artery.

The predominant bacterial pathogens were enteric aerobic gram-negative bacilli and gram-positive cocci (26). In our patients, the most common pathogens isolated from liver aspirates were *E. coli* sensitive to third-generation cephalosporin.

Recent studies of the new agent tacrolimus (FK506) have shown a reduction in bacterial infections in comparison with patients treated with cyclosporine. This effect is probably due to a reduction in the total steroid dosage and serotherapy used for rejection episodes, and the number of rejection episodes encountered (27). In our study, 3 cases (case 1, 2, 4) were taking tacrolimus.

Ultrasonography is the primary imaging modality for the evaluation of liver abscess (24), because it is safe, accurate, and a noninvasive method of demonstrate and evaluate nonvascular complications concerning the hepatic parenchyma and extrahepatic tissues (25). In our series, the first modality for diagnosing liver abscess was in the US. In 1 case, a computed tomography scan was done owing to suspicion of a US operator about number of abscesses.

Colona and associates suggest the following risk factors for infection after transplant: (1) age, > 20 years, (2) biliary atresia, (3) lower preoperative albumin level, (4) gastrointestinal or vascular complications, (5) requirement for postoperative hemodialysis, and (6) longer stay in the intensive care unit after surgery (26). Postrenal transplant hypoalbuminemia (< 3.5 g/dL) was considered to be a risk factor for *cytomegalovirus* infection, graft loss, and increase mortality (28). In our series, all patients had hypoalbuminemia (< 3.5 g/dL) which is also seen in other studies (14, 18). Prolonged international normalized ratio and increase in alkaline phosphatase were seen in 80% and 100% of patients, respectively. Increase in total bilirubin was seen in 80% of patients (Table 2).

In patients with intrahepatic abscesses, computed tomography, or US-guided percutaneous, transhepatic drainage is indicated. Using this

interventional management, the septic status of patients can resolve within several days or weeks. Recovery of patients or retransplant, planned in an elective manner depends on the severity of disease and success of interventions (5). In our study, percutaneous drainage, together with intravenous antibiotic therapy was used for 3 patients; however, case 4 and case 5 underwent open drainage due to bowel obstruction and failure of 2 times percutaneous drainage, respectively.

The mortality rate was different in studies from 10% (29) to 40% (14). The causes of death included multiple-organ system failure due to sepsis and respiratory insufficiency due to overwhelming pneumonias (especially with antibiotic-resistant pseudomonas) (14, 29). Mortality was seen in 2 cases (40%) in our study and was due to massive bleeding and liver failure (case 2), and sepsis and multiorgan failure (case 5).

Conclusion

Hepatic abscess, a rare complication after liver transplant, was associated with hepatic artery thrombosis and biliary anastomosis strictures. Mortality was higher compared with patients who had not undergone transplant. Prolonged antibiotic therapy and drainage are required to improve the outcome in these patients.

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