

## A Tale of Two Abscesses: A Case Report of Recurrent Pyogenic Liver Abscess Formation after Successful Liver Transplantation

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Received: 10 Apr 2023

Accepted: 10 May 2023

Published: 17 May 2023

J Short Name: ACMCR

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### Citation:

Ho R, A Tale of Two Abscesses: A Case Report of Recurrent Pyogenic Liver Abscess Formation after Successful Liver Transplantation. *Ann Clin Med Case Rep.* 2023; V10(21): 1-5

### Keywords:

Immunosuppression; Cholangiopathy; Tacrolimus

## 1. Abstract

The development of pyogenic liver abscess (PLA) after liver transplant is rare. Studies have commonly reported hepatic artery thrombosis and biliary tract pathologies as risk factors for PLA formation. Whilst other modifiable etiologies include diabetes and immunosuppression. This is a case of a 71-year-old male with a history of hepatitis B, diabetes mellitus, and hepatocellular carcinoma who presented with PLA formation 14 years and 21 years after successful liver transplantation without biliary tract reconstruction. Post-transplant biliary cholangiopathy and hepatic artery thrombosis were not present in both instances. Intravenous antibiotics and abscess drainage were performed for both PLAs with complete resolution. This case highlights the importance of early recognition of liver abscess and management of diabetes mellitus glycemic control, immunosuppressive drugs, and perioperative antibiotics prophylaxis to prevent future PLA formation in post-liver transplant patients.

## 2. Introduction

Liver abscess is a rare disease in the U.S with an incidence rate of 2.3 cases per 100,000 people [1]. There is a predominance of disease occurrence in males and a peak incidence between 50-60 years old [2]. Liver abscesses present insidiously in patients after liver transplant (LT) because most occurrences are due to biliary strictures and cholangiopathy often related to hepatic artery thrombosis (HAT). These abscesses can occur several months up to several years after transplant depending on the course of de-

velopment of cholangiopathy and cholangitis. While diabetes and immunosuppression are contributing factors, there are far fewer cases of liver abscesses with these as the primary risk factor. There is a paucity of studies on predictive factors and presentation of liver abscess after successful liver transplantation. We describe an unusual presentation of a patient with no known cholangiopathy or antecedent cholangitis who developed primary liver abscesses 14 and 21 years after initial liver transplantation.

## 3. Case Presentation

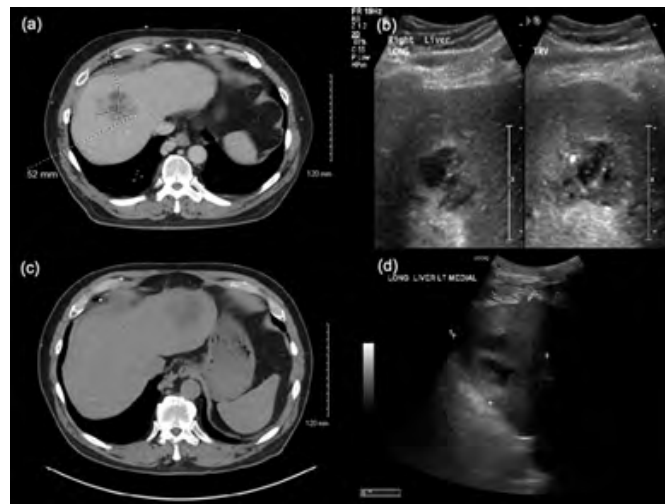
The patient is a 71-year-old Irish Japanese male who was diagnosed with hepatitis B when he was attempting to donate blood in the 1970s. His disease was quiescent for several years, but he had an episode of reactivation eight years after diagnosis. He underwent an interferon-based treatment for three months and was subsequently managed with oral antiviral agents. In 2001, surveillance testing identified a 5 cm liver mass suspicious for hepatocellular carcinoma and an alpha fetoprotein of 117 ng/dL. He underwent trans-arterial chemoembolization and was evaluated for LT because of underlying cirrhosis with portal hypertension. A successful liver transplantation was performed in 2002. Since that time, he has had no evidence of recurrent cancer and has had no rejection episodes on maintenance immunosuppression with tacrolimus. On several occasions the patient had reactivation of hepatitis B but recently has been well controlled on tenofovir alafenamide. He has a long history of diabetes and hyperlipidemia prior to transplantation and recently developed chronic kidney disease, stage 3

likely related due to long-term diabetes and calcineurin inhibitor use. Patient did not have a history of illicit drug use and had no recent history of travel abroad.

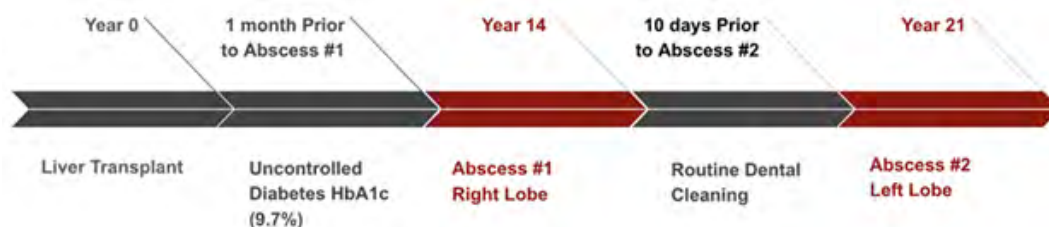
Fourteen years post-liver transplantation, the patient developed fever, chills, diarrhea, and emesis for a week. This occurred about a week after multiple exposures to individuals with upper respiratory infections. His most recent HbA1c levels from one month prior was 9.7%. He was found to have elevated liver enzymes and CT scan showed a 5.2 cm x 4.2 cm hypodense mass in the right hepatic lobe (Figure 1a). Ultrasound-guided aspiration of the mass yielded 12 mL of brownish cloudy fluid (Figure 1b). Biopsy samples yielded cytologic smears and cell blocks of necrosis and marked inflammation in a background of normal hepatocytes, consistent with hepatic abscess. The blood and abscess culture grew *Klebsiella pneumoniae*. The clinical picture and laboratory studies confirmed a diagnosis of liver abscess and was initially given intravenous (IV) vancomycin and cefepime but was discharged on ceftriaxone after the final sensitivities returned. His liver tests and imaging studies returned to baseline two months later.

He had no subsequent illnesses until seven years later (21 years after the transplant) until he was noted to have mild elevation in alanine aminotransferase (ALT) to 58 IU/L. Liver biopsy was performed and revealed 5% macrosteatosis, no inflammation, no

fibrosis, and no evidence of rejection. A few months later, he presented with fever, chills, rigors, and sweating. He had routine dental cleaning 10 days prior and took prophylactic oral amoxicillin. After this, he had diarrhea for 3 days and was thought to have gastroenteritis. He did not appear toxic and was found to have procalcitonin of 1.04 ng/mL, alkaline phosphatase 394 IU/L, aspartate aminotransferase 33 IU/L, alanine aminotransferase 60 IU/L, and gamma-glutamyl transferase 415 IU/L. His HbA1c levels from 1.5 months prior was 7.1%. He was placed on empiric intravenous vancomycin and cefepime. An abdominal CT scan demonstrated a 2.4 X 4.3 X 5 cm abscess or mass in the left hepatic lobe (Figure 1c). Ultrasound showed 6.5 cm X 6.5 cm complex cystic lesion in lateral segment of liver, suggesting an abscess (Figure 1d). He underwent ultrasound guided aspiration and drainage tube placement. A total of 15 mL of purulent aspirate was obtained through the drain. The abscess culture yielded *Klebsiella Oxytoca*, *E coli* and *Streptococcus Constellatus*. He was placed on intravenous ertapenem for 6 weeks. Subsequent imaging showed partial resolution of the abscess and the drainage tube was removed a few weeks later. In both PLA occurrences described above, the patient had no history of biliary reconstruction, biliary tract disease or HAT. He had no other extrahepatic manifestations associated with the PLA besides the aforementioned signs. The timeline of events is noted in Figure 2.



**Figure 1:** Computed tomography (CT) scan of the patient’s liver showing (a) 5.2 x 4.2 cm abscess in right lobe, (b) ultrasound scan of the liver shows 4.4 x 3.2 x 3.8 cm abscess in right lobe, (c) CT scan of the liver shows 2.4 X 4.3 X 5 cm abscess in left lobe, (d) ultrasound scan of the liver shows 6.5 cm X 6.5 cm abscess in left lobe.



**Figure 2:** Timeline of Events

## 4. Discussion

The majority of liver abscesses in the United States and other Western countries are classified as pyogenic (bacterial) followed by amebic and more rarely fungal infections [4]. Pyogenic liver abscesses (PLA) are often polymicrobial with the common organisms being *Klebsiella*, *E. coli*, *Streptococcus*, and anaerobes [3]. Oftentimes, liver abscesses are cryptogenic, with no obvious origin of infection. The most common identifiable cause of PLA is due to biliary tract infection (30-50%) including gallstone disease, obstructing tumors, and strictures. Known risk factors include diabetes mellitus, liver surgery/transplant, liver cirrhosis, malignancy, immunosuppression, chronic use of proton pump inhibitors (PPI), and advanced age [4].

Diabetes mellitus is a strong, modifiable risk factor of PLA formation and is highly associated with *Klebsiella pneumoniae* infection; although primarily described in patients in East Asian countries, there is a rising incidence in the United States [5, 6]. Thomsen et al found that individuals with diabetes had a 3.6-fold increased risk of experiencing PLA, compared with population control subjects (adjusted relative risk, 3.6; 95% confidence interval, 2.9–4.5) [5]. This is likely due to altered immunity in diabetic patients and subsequent impaired host defense mechanisms and increased susceptibility to infections. Fung et al investigated the association of glycemic control with clinical outcomes in *Klebsiella pneumoniae* liver abscess [7]. They found that patients with uncontrolled glycemia (HbA1c  $\geq$  7%) had a higher rate of gas-forming liver abscess, cryptogenic liver abscess and metastatic infection than those with controlled glycemia. Thus, it was not unusual to see that our patient with long standing diabetes and on immunosuppressants developed *Klebsiella* PLA with no underlying cause.

Patients who have undergone liver transplantation are at a higher risk of developing PLA. To assess the incidence of liver abscess formation, a literature review was performed on studies that described PLA in the LT population (8-13) (Table 1). The reported incidences ranged from 0.9%-3% and median time for PLA formation ranged from 2 months to over 3 years. Most PLAs occur within the first several years post liver transplantation. Recurrence of PLA among LT patients has been demonstrated to occur within a year of the first incidence [11,12]. Unlike most cases reported in literature, PLA formation in our patient developed decades after liver transplantation and another PLA recurred seven years later.

The vast majority (~95%) of PLA cases after LT occurred in the setting of biliary strictures, cholangiopathy or previous Roux-en-Y reconstruction [8-13] (Table 1). This is likely due to perturbations of the biliary tract related to vascular insufficiency, inflammation, or postoperative healing and fibrosis. In hepaticojejunostomy reconstruction, the removal of the biliary sphincter increases the risk of reflux of intestinal bacteria into the biliary tree. Interestingly, our patient had nonspecific symptoms in the absence of biliary strictures, cholangiopathy, or ischemia.

Long term immunosuppression in post LT patients is another important risk factor for PLA formation. Dental, endoscopic, and other procedures may potentially lead to transient bacteremia. In this case, our patient had a routine dental cleaning procedure 10 days prior to development of PLA in the absence of uncontrolled diabetes and biliary tract pathology. Both *Klebsiella Oxytoca* and *Streptococcus Constellatus* are naturally found in oral flora as well as the intestinal tract, suggesting that the patient's prior dental cleaning despite taking prophylactic antibiotics might have predisposed him to the recurrent PLA formation. PLA formation after routine dental cleaning is rare in a healthy individual with only a few cases reported in the literature [14, 15]. Cases in which patients develop PLA in shorter periods of time have been reported in the literature (7 and 10 days), however, these patients have undergone more invasive procedures including root canal filling and dental prosthesis implantation [16, 17]. Given the patient's long-term maintenance on immunosuppressive drugs, he was at a heightened risk of developing systemic infections from an oral source and may have facilitated development of his PLA. Dental considerations in post-liver transplant patients include adhering to the American Heart Association regimen for prophylactic antibiotic coverage [18].

Patients with PLA regardless of a previous transplant, have quite similar imaging presentation and management. Lefort et al compared 14 post LT patients with PLA from 541 LT patients and 42 non-LT patients with PLA [9]. They found no significant difference in their clinical, radiological, microbiological characteristics, PLA drainage rates and antibiotic therapy duration but there was a pattern of increased diabetic patients and less acute presentation in post liver transplant patients with PLA. In previous large series, empiric broad spectrum antibiotic therapy was initiated in all cases [8-13] (Table 1). The antibiotic regimen was later tailored after cultures and susceptibility were made available. Percutaneous drainage was performed dependent on the patient's medical condition and size of the abscess. Imaging modalities including ultrasound, CT scan, and MRI were used to evaluate resolution of abscess. Patients received intravenous antibiotics treatment for at least 2 weeks and percutaneous drainage was performed for 62%-92% of patients. Concurrent with prior literature, our patient was started on IV antibiotics, underwent ultrasound-guided aspiration, and was discharged on antibiotics for his first PLA. CT scan confirmed resolution of abscess after 2 months. The patient's second PLA followed a similar management plan with empiric IV antibiotics, followed by ultrasound guided aspiration and drainage. His antibiotic regimen was then tailored to the abscess culture results and subsequently discharged with IV antibiotics and a drainage tube. Drain tube was removed 10 days later and CT scan confirmed near resolution of abscess after 1.5 months.

The natural course and outcomes of PLA in LT patients remain under investigation. PLA in LT patients is associated with increased risk of hepatic complications, including ischemic cholangitis and

cholangiopathy secondary to HAT [8-13] (Table 1). Both of which predispose patients to re-transplantation likely related to cholangiopathy and recurrent infection. The need for re-transplantation ranges from 0%-35.7% in patients who have had PLA [8-13] (Table 1). Additionally, Czerwonko et al. Demonstrated a marked

lower five-year survival rate in LT patients with PLA in comparison to their counterparts, LT patients without PLA (49% vs 89%,  $p<0.001$ ) [8]. Our patient has survived for seven years without requiring re-transplantation after the initial liver abscess. The second liver abscess was also resolved without further complications.

**Table 1:** Post-liver Transplant Abscess Formation Literature Review

Author, year	Case (Incidence)	Time from LT to PLA (range)	Predisposing factors	Management	Outcome
Czerwonko, 2018 [8]	26/879 (3%)	11.8 mo (0.57–246)	23/26 hepatobiliary surgery 20/26 Post-LT biliary strictures 7/26 HAT	<b>IV antibiotics:</b> 8/26, 4 weeks <b>Percutaneous drainage:</b> 16/26	<b>Death:</b> 4/26 <b>Re-transplantation:</b> 3/26 <b>Recurrent PLA:</b> 7/22
Lafont, 2020 [9]	not reported	34.5 mo (0.5-132)	13/14 ischemic cholangitis due to HAT	<b>IV antibiotics:</b> 14/14, median duration 6.5 [3-23] weeks <b>Percutaneous drainage:</b> 11/14	<b>Death:</b> 4/14 <b>Re-transplantation:</b> 5/14 <b>Recurrent PLA:</b> 8/14
Justo, 2018 [10]	14/984 (1.5%)	39.7 mo (1.6–285)	11/14 Biliary strictures 8/14 HAT 2/14 Roux-en-Y	<b>IV antibiotics:</b> 11/14 for 2 weeks; 3/14 for 4 weeks <b>Percutaneous drainage:</b> 11/14	<b>Death:</b> 3/14 <b>Re-transplantation:</b> 2/14 <b>Recurrent PLA:</b> n/a
Nikeghbalian, 2009 [11]	5/560 (0.9%)	2 mo (30-240)	3/5 biliary stricture 2/5 diabetes 1/5 with HAT	<b>IV antibiotics:</b> 5/5, mean duration 6 weeks <b>Percutaneous drainage:</b> 4/5 <b>Repeat drainage:</b> 2/5	<b>Death:</b> 2/5 <b>Re-transplantation:</b> 0/5 <b>Recurrent PLA:</b> n/a
Tachopoulou, 2003 [12]	12/459 (2.6%)	12.7 mo (0.83-140)	8/14 HAT 8/14 cholangitis 3/14 Roux-en-Y 2/14 liver biopsy 1/14 cryptogenic 1/14 stricture 1/14 fungal arteritis	<b>IV antibiotics:</b> 12/12, mean duration 6 weeks <b>Percutaneous drainage:</b> 11/12 <b>Repeat drainage:</b> 7/12	<b>Death:</b> 5/12 <b>Re-transplantation:</b> 5/12 <b>Recurrent PLA:</b> 2/14
Kornasiewicz O et al., 2016 [13]	15/1100 (1.4%)	7.2 mo (1–143)	8/15 Biliary stricture 6/15 Roux-en-Y 5/15 HAT or stenosis	<b>IV antibiotics:</b> 5/15 for 2 weeks <b>IV antibiotics (2wks)+percutaneous drainage:</b> 10/15	<b>Death:</b> 5/15 <b>Re-transplantation:</b> 2/15 <b>Recurrent PLA:</b> 3/15

## 5. Conclusion

This case illustrates that liver abscesses should be considered in LT patients with nonspecific symptoms or unexplained elevations in liver enzymes even in the absence of previous biliary reconstruction or cholangiopathy. Long-term immunosuppression and diabetes (whether immunosuppression related or not) are important risk factors. As more patients are living longer after liver transplantation and with reduced immunosuppression over time, we may expect more of these patients to have infectious complications that reflect the general population and may not be directly related to the technical nuances of the transplant procedure. Early recognition of liver abscess and prompt management with drainage and antibiotics are essential to prevent septic and systemic sequelae. Reducing immunosuppression, optimizing glycemic control and administration of peri-procedure prophylactic antibiotics may potentially be helpful in prevention of PLA but this would need to be explored in a larger series.

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