Diagnosis and Treatment of Acute Appendicitis After Orthotopic Liver Transplant in Adults

Linwei Wu,[1] Jianwei Zhang,[2] Zhiyong Guo,[1] Qiang Tai,[1] Xiaoshun He,[1] Weiqiang Ju,[1] Dongping Wang,[1] Xiaofeng Zhu[1]

Abstract

Objectives: **The incidence of acute appendicitis after orthotopic liver transplant is low but difficult to differentiate from other posttransplant complications. We sought to summarize the clinical characteristics, diagnosis, and treatment of acute appendicitis during the early posttransplant stage.**

Materials and Methods: **Data from 4 liver transplant recipients with acute appendicitis immediately after transplant and 4 patients with misdiagnosed appendicitis, between January 2000 and December 2007, were studied retrospectively.**

Results: **The incidence of acute appendicitis immediately after orthotopic liver transplant was 0.49%. Four patients had right lower quadrant abdominal pain with fixed tenderness, rebound tenderness, and fever on the eighth, ninth, 11th, and 13th days after surgery. White blood cells counts were elevated in all patients. Appendectomies were performed on day 1 or 2 after the onset of symptoms. No appendicular perforations were found. All patients recovered well. After an exploratory laparotomy, the 4 patients originally misdiagnosed with appendicitis were correctly diagnosed with a duodenal diverticulum perforation (1 patient), a jejunum perforation (1 patient), and bile leakage (2 patients). Two of these patients died despite aggressive treatment.**

Conclusions: **The incidence of acute appendicitis immediately after orthotopic liver transplant is low and should be differentiated from other surgical complications, such as gastrointestinal perforation and bile leakage. Appendectomy is recommended in these patients as early as possible.**

Key words: *Transplantation, Inflammation, Complication, Prognosis, Appendectomy*

The inflammatory response in recipients after orthotopic liver transplant (OLT) is more complicated owing to immunosuppression. Acute appendicitis, a common abdominal complication, rarely occurs after OLT, but when it does, it might be confused with other gastrointestinal complications.[1] Only a few cases of acute appendicitis after OLT have been reported. Here, we discuss the clinical course of 4 OLT recipients with acute appendicitis and 4 other patients (who were misdiagnosed with appendicitis) and summarize the clinical characteristics, diagnosis, and treatment of acute appendicitis after OLT.

Patients and Methods

Eight hundred seventeen OLTs were performed at our hospital between January 2000 and December 2007 (694 male, 123 females; mean age, 49.5 ± 16.3 years; age range, 18-75 years). Of these, 402 were due to liver cirrhosis from hepatitis B or hepatitis C, 299 had primary hepatocellular carcinoma (with or without cirrhosis), 96 had severe hepatitis, and 20 had another disease(s).

Different transplant techniques were done according to the recipient's condition including 151 classic OLTs (36 received a venous bypass, and 32 received a modified method [previously described]),[2] 598 modified piggybacks, and 68 classic piggybacks. Immunosuppression after the transplant included a

From the [1]Department of Organ Transplantation of First Affiliated Hospital, Sun Yat-sen University and [2]Zhongshan Medical School of Sun Yat-sen University, Guangzhou, China

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Address reprint requests to: *Xiaoshun He, Department of Organ Transplantation of the First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China*
Phone: *+862087755766* ***Fax:*** *+862087306082* ***E-mail:*** *gdtrc@163.com*

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double regimen (steroids, and tacrolimus or cyclosporine) or a triple regimen (steroid, tacrolimus or cyclosporine, and mycophenolate mofetil). Steroids were withdrawn as follows: 500 mg methylprednisolone (intraoperatively), 60 mg IV every 6 hours (day 1), 50 mg every 6 hours (day 2), and then tapered 40 mg every day from the third day after surgery until day 7. Intravenous use of methylprednisolone was converted to oral tablets on day 8, tapered 8 mg every 3 days, maintained at 4 mg, and discontinued 3 months after surgery. Interleukin-2 receptor monoclonal antibody induction was used in high-risk patients including those aged older than 60 years, and those with hypoproteinemia, severe hepatitis, retransplant, and hepatorenal syndrome. Liver functioning and blood concentration of the immunosuppressants were monitored after surgery.

Each organ donation and transplant was approved by our local institutional ethics committee, and conformed with the ethical guidelines of the 1975 Helsinki Declaration. The demographics and clinical characteristics of the 4 recipients with acute appendicitis posttransplant and the 4 patients with misdiagnosed appendicitis are shown in Table 1.

Results

Clinical features of recipients with acute appendicitis

All patients received routine follow-up after discharge (mean follow-up, 49.6 months; range, 1 day to 112 months). The incidence of acute appendicitis after OLT was 0.49%. The 4 patients with acute appendicitis all recovered well with excellent graft function during the early stage after transplant. They complained of abdominal pain and fever on days 8, 9, 11, and 13 posttransplant (their temperatures were 37.8°C, 38.3°C, 38.5°C, and 38.6°C). Results of a physical examination revealed fixed tenderness and rebound tenderness of the right abdominal quadrant in 2 patients and of the entire abdomen in the remaining 2 patients. None of the patients had vomiting, diarrhea, anorexia, or any other gastrointestinal symptom(s). The white blood cells counts were elevated to $17 \times 10^9/L$ and $19 \times 10^9/L$ in 2 patients with abdominal pain, while in the remaining 2 patients they were within the normal range on the first day but increased to $18 \times 10^9/L$ and $21 \times 10^9/L$ two days after the onset of abdominal pain. The results of the liver function and biochemical tests were normal in all of the 4 patients. No abnormalities were found on x-ray films or ultrasonography, except that 2 patients had swelling of the appendix and thickening of the appendix wall on ultrasonography.

Clinical manifestation of misdiagnosed patients

The 4 misdiagnosed patients complained of abdominal pain and fever on days 8, 9, 10, and 11 posttransplant, with the highest temperature being 38.5°C, 37.8°C, 38.6°C, and 38.3°C. Results of a physical examination demonstrated fixed tenderness and rebound tenderness of the right abdominal quadrant in 3 patients and of the entire abdomen in the remaining patient. White blood cells counts were elevated to $19 \times 10^9/L$, $18 \times 10^9/L$, $21 \times 10^9/L$, and $23 \times 10^9/L$ in the 4 patients on day 2 or 3 after the onset of abdominal pain. No abnormalities were found on x-ray films or ultrasonography. After an exploratory laparotomy, the 4 patients originally misdiagnosed with appendicitis were correctly diagnosed with a duodenal diverticulum perforation (1 patient), a jejunum perforation (1 patient), and bile leakage (2 patients).

Treatment and outcome

Appendectomy was performed on day 1 (2/4) or day 2 (2/4) of the onset. Immunosuppressive therapy was maintained during the perioperative period.

Table 1. Demographic and clinical characteristics of appendicitis patients and misdiagnosed patients.

Complications	Patient	Sex	Age (y)	Primary diseases	Preoperative MELD score	Surgical method	Immunosuppressive regimen
Appendicitis patients	1	M	63	HCC	21	Modified piggyback	Doublet regimen
	2	M	33	HBV-related liver cirrhosis	32	Modified piggyback	Induced regimen
	3	M	49	HBV-related liver cirrhosis	27	Modified piggyback	Doublet regimen
	4	F	21	Hepatic epithelioid hemangioendothelioma	16	Modified piggyback	Doublet regimen
Misdiagnosed patients							
	1	M	49	HCC	19	Classic OLT	Doublet regimen
	2	M	53	HCC, Liver cirrhosis	31	Modified piggyback	Doublet regimen
	3	M	39	Severe hepatitis B	40	Classic piggyback	Induced regimen
	4	M	56	HCC	22	Classic OLT	Triple regimen

Abbreviations: F, female; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; M, male; MELD, model for end-stage liver disease

Liver grafts function remained normal during the perioperative period of appendectomy. All of the 4 patients recovered well and as of this writing, have been followed up for 84, 62, 40 and 29 months, respectively. The 4 misdiagnosed patients received appropriate surgical procedure after exploratory laparotomy. Management and the outcome of the above patients are shown in table 2.

Discussion

Liver transplant is the most-effective option for end-stage liver disease. More and more patients are achieving long-term survival, with excellent graft functioning and quality of life. Meanwhile, some relatively rare complications have been found and have attracted clinical interest. Gastrointestinal bleeding, intestinal obstruction, intestinal perforation, and acute appendicitis have all been reported after solid organ transplant.[3] In persons without immunosuppression, acute appendicitis is a common abdominal condition, and appendectomy is the treatment of choice. However, in liver transplant recipients, acute inflammation is atypical owing to the use of immunosuppressive therapy, and acute appendicitis is easily confused with other complications. Additionally, for its low incidence after OLT, appendicitis is easily ignored—there is a paucity of related experiences in the literature—and this increases the difficulty of appropriately diagnosing and treating it. Interestingly, however, the 4 patients with acute appendicitis reported in this study presented with typical manifestations, indicating that the inflammatory response could not be suppressed by the immunosuppression in some patients. We may underestimate the incidence of acute appendicitis because some patients with it may be asymptomatic and may be relieved spontaneously while taking immunosuppressive agents and antibiotic prophylaxis.

It has been reported that the incidence of acute appendicitis after renal transplant is 0.09%-0.60%.[4, 5] However, with only few case reports, it is difficult to have an accurate prevalence of appendicitis after OLT. Abt reported 8 patients with acute appendicitis after liver transplant, the largest number of cases to date. He found the incidence of acute appendicitis after OLT to be 0.09%[6]; the patients experienced appendicitis 3 weeks to 181 months after OLT. Similar to nonimmunosuppressed patients, the cause of acute appendicitis after transplant included obstruction of the appendix cavity and bacterial overgrowth owing to high pressure in the cavity. In some liver transplant recipients, lymphocytosis may increase pressure in the appendix cavity after an operation. The most-common opportunistic pathogen after solid organ transplant is *cytomegalovirus.* Gastrointestinal *cytomegalovirus* also increases the likelihood of acute appendicitis.[3, 6] (The incidence of appendicitis after liver transplant at our center was 0.49%.) In our study, the patients had acute appendicitis early in the postoperative period, while nobody had it during long-term follow-up, which does not agree with a previous report.[6] The incidence rate seems higher in the Abt study during the early stage after the operation. However, risk factors remain unclear. The higher incidence rate in his study might be

Table 2. Surgery and outcome of appendicitis patients and misdiagnosed patients.

Complications	Patients	Anesthesia	Incision	Diagnosis	Surgical method	Pathology	Follow-up (mo)	Outcome
Appendicitis patients	1	SEA	AI	AA	Appendectomy	Simple appendicitis	84	Survival
	2	GA	EI	AA	Appendectomy	Suppurative appendicitis	62	Survival
	3	SEA	AI	AA	Appendectomy	Suppurative appendicitis	40	Survival
	4	SEA	AI	AA	Appendectomy	Simple appendicitis	29	Survival
Misdiagnosed patients	1	GA	EI	Duodenal diverticulum perforation	Diverticulum resection	None	68	Survival
	2	SEA to GA	AI to EI	Jejunum	Partial jejunum perforation	None resection	Severe infection after reoperation and died 15 days later	
	3	GA	EI	Bile leakage	Repairing and drainage	None	Nasobiliary drainage through ERCP after surgery, biliary fistula healing 2 months later, survival	
	4	SEA to GA	AI to EI	Bile leakage	Repairing and drainage	None	Biliary fistula nonhealing, complicated with ischemia of bile duct, died of liver failure 4 months after surgery	

Abbreviations: AI, appendix incision; EI, exploratory incision; ERCP, endoscopic retro grade cholangiopancreatography; GA, general anesthesia; SEA, Spinal-epidural anesthesia

attributable to manipulation of the bowel during the operation or postoperative stress. The difference in the incidence of acute appendicitis after OLT and other abdominal operations remains unclear, because only a few cases of acute appendicitis after abdominal surgeries have been reported.

In the existing case reports of acute appendicitis after OLT, clinical manifestation was similar to nonimmunosuppressed patients. Most patients had nonspecific gastrointestinal symptoms such as nausea and vomiting. Fever was present in most instances. Fixed tenderness and rebound tenderness of the right abdominal quadrant were the most-common signs. However, unlike nonimmunosuppressed patients, the white blood cell counts were not elevated in some liver transplant recipients. With immunosuppression, particularly with the use of a steroid, the inflammation was not easily limited, and the clinical symptoms were atypical. Therefore, appendicitis after a liver transplant should be diagnosed cautiously. Ultrasound should be routine. Swelling of the appendix cavity and thickening of the appendix wall are common findings on ultrasound. Besides, ascites and forming of a circumscribed abscess in the peritoneal cavity also may be seen.

Because of the atypical presentation and the presence of some graft-related complications, it is difficult to make a clear-cut diagnosis of acute appendicitis after abdominal solid organ transplant. In renal and pancreas transplant recipients, the graft is placed in the right iliac fossa. Acute appendicitis is easily confused with the graft-related complications, such as infection, rejection, and thrombosis.[7-10] In patients with right lower quadrant abdominal pain and fever after OLT, the diagnosis of bile leakage and gastrointestinal perforation should be considered. Bile leakage is a common biliary complication, and the incidence of gastrointestinal perforation is not low, especially in patients with retransplant or a history of an epigastrium operation. When bile leakage or gastrointestinal perforation occurs after OLT, bile or the intestinal contents would be limited in the right lower quadrant abdomen, which would lead to tenderness and rebound tenderness of right lower quadrant abdomen. Therefore, the differential diagnosis should be made according to clinical manifestation(s) and ultrasound or computed tomography scanning.[11-13] Computed tomography scanning is a helpful diagnostic tool for posttransplant abdominal pain concerning sensitivity (94%) and specificity (94%).[14] However, there are several reasons why we did not conduct a computed tomography scan for the suspected patients in this study.

First, bedside computed tomography scanning cannot be performed in our hospital at this time, which limits the ability of recipients to have an examination while still sick immediately after the transplant. Second, several years ago, computed tomography scanning had to be done by appointment, and we could not arrange for a computed tomography scan on an emergent basis at that time. Third, and most important, ultrasound study by an experienced examiner can be as accurate as a computed tomography scan is in diagnosing appendicitis (83% sensitivity, 93% specificity).[14-16] Bedside ultrasound is easy to perform and routinely practiced. Therefore, ultrasound was the most important diagnostic tool in this study. However, we do believe a computed tomography examination, with increased use, would be greatly helpful in diagnosing abdominal pain on an emergent basis, in a person who has undergone a liver transplant.

Appendicular abscess is rare in liver transplant recipients because of immunosuppression. If ascites are found on image examination, bile leak and gastrointestinal perforation should be highly suspect. In this situation, an ultrasound-guided abdominal puncture is helpful. However, because of the limitation of ultrasound's sensitivity, patients who have a perforation or bile leakage may have only a few ascites and these will not be detected. The 4 misdiagnosed patients in our study had symptoms of appendicitis without having an abnormality on imaging examination. In patients with a high risk of biliary leakage or gastrointestinal perforation, the diagnosis should be made more cautiously when the patient presents with abdominal pain after the operation. Oral methyl blue may be helpful in making the diagnosis.[17]

Development of appendicitis after a liver transplant is fast and could easily perforate without immediate treatment. When using broad-spectrum antibiotics, preoperative preparation should also be considered. An appendectomy is the most-effective treatment and is strongly recommended. In the literature, all of the patients with appendicitis after transplant underwent an appendectomy and recovered well.[6, 18] The incision was made according to the clinical status. In patients with a definite

diagnosis, an appendix incision should be chosen under epidural anesthesia. While in patients with a doubtful diagnosis, considering the low incidence of appendicitis after a liver transplant and the possibility of other surgical emergencies, an exploratory incision is better.

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