Gastrointestinal Perforations in Adult Whole-Liver Transplant Patients: Clinical, Radiologic, and Histopathologic Analysis

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ABSTRACT

Background. Gastrointestinal perforation (GIP) is a rare complication after adult liver transplant (LT) associated with high morbidity and mortality. Limited data are available about clinical risk factors and underlying pathogenic mechanisms.

Methods. The retrospective study included all GIP cases from a consecutive cohort of 361 LT recipients during the period 2005-2017. Clinical variables were investigated as potential risk factors for GIP, and radiologic and histopathologic evaluations were undertaken to identify any causative mechanism.

Results. A total of 22 patients developed at least 1 episode of GIP (prevalence 6.1%) at a median time of 18.5 [interquartile range, 12.5-28.5] days after LT. The perforations occurred in the small bowel (63.6%), transverse colon (27.3%), right colon (22.7%), left colon (9.1%), and stomach (9.1%). A total of 27.3% of patients developed multiple sites of GIP, and in 31% GIP recurred after curative surgery. The 30-day mortality rate after relaparotomy was 40%. A history of previous abdominal surgery (odds ratio, 2.5) and early post-LT relaparotomy due to other complications (odds ratio, 2.6) were significant risk factors for GIP. No thromboembolic or steno-occlusive complications of any splanchnic vessel were detected at computed tomography scan, while histopathology examination on perforated gastrointestinal segments excluded cytomegalovirus infection, graft-vs-host disease, and inflammatory bowel disease. In all the cases, ischemic necrosis with aspecific microangiopathy and microembolization were the pathologic features detected.

Conclusions. GIP is a severe complication after LT with frequent multiple gastrointestinal involvement and recurrence after curative surgery. The pathologic underlying mechanism is usually microvascular ischemia. Clinical risk factors are history of previous abdominal surgery and early post-LT relaparotomy.

GASTROINTESTINAL perforation (GIP) is a rare complication after liver transplant (LT), with a reported incidence of 1% to 5.3% in adult recipients and 8.3% to 14% in pediatric recipients [1,2]. The higher incidence in children than in adults is most likely due to tight bowel adhesions formation during previous portoenterostomy. It may occur at any point in the gastrointestinal (GI) tract, including stomach, jejunum, ileum, and colon and is associated with potentially high mortality and morbidity. The causes of GIP after LT are unclear and probably multifactorial. In pediatric cases, suspected risk factors include previous abdominal surgery (ie, the Kasai

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Table 1. Patients Demographic and Clinical Characteristics, Operative Details, and GIP and Re-GIP Features

Patients' Demographic and Clinical Characteristics and Operative Details	
	Total (N = 22)
Age, median, (IQR), y	59 (50-61)
Male:female	18:4
BMI median, (IQR)	26.3 (25-28)
Previous abdominal surgery, No. (%)	8 (36.4)
Diabetes, No. (%)	3 (13.6)
MELD score, median (IQR)	15 (13-19)
Spontaneous bacterial peritonitis episodes, No. (%)	3 (13.6)
Esophageal varices, No. (%)	5 (22.7)
Refractory ascites, No. (%)	6 (27.2)
HCC diagnosis, No. (%)	10 (45.5)
Causes of cirrhosis, No. (%)	
- Alcohol	8 (36.4)
- Viral hepatitis	10 (45.5)
- Autoimmune	2 (9.1)
- Other	2 (9.1)
HIV positivity, No. (%)	4 (18.2)
IgG CMV +/IgM CMV +, No. (%)	18 (81.8)/3 (13.6)
Urgent LT, No. (%)	2 (9.1%)
Cold IT, mean (SD), min	483.6 (175.6)
Warm IT, mean (SD), min	43 (12.9)
Operative time, mean (SD), min	432.9 (131)
Portal clamp time, mean (SD), min	68.6 (20.4)
Type of outflow reconstruction, No. (%)	
- Piggyback	17 (77.3)
- Side-to-side cavocavostomy (Belghiti)	3 (13.6)
- Caval replacement (classical)	2 (9.1)
Roux-en-Y choledochojejunostomy, No. (%)	1 (4.5)
Aortohepatic jump, No. (%)	2 (9.1)
Delayed laparotomy closure after LT, No. (%)	2 (9.1)
Packed red blood cells, mean (SD), IU	7.7 (5.8)
Plasma, mean (SD), mL	2330 (2067.3)
ICU LOS, median (IQR), d	5 (4-6)
Delayed laparotomy closure after LT, No. (%)	2 (9.1)
GIP Features	
Time interval between LT and perforation, median (IQR), d	18.5 (12.5-28.5)
Post-LT pre-GIP relaparotomy, No. (%)	7 (31.8)
Causes of relaparotomy, No. (%)	
- Bleeding	4 (57.1)
- Biliary leak	3 (42.9)
- Intestinal occlusion	1 (14.3)
GIP during ICU stay, No. (%)	6 (27.3)
Associated biliary complications, No. (%)	3 (13.6)
Enteral liquid in peritoneum, No. (%)	15 (68.2)
Multiple sites of perforation, No. (%)	6 (27.3)
Sites of perforation, No. (%)	
- Jejunum/ileum	14 (63.6)
- Transverse colon	6 (27.3)
- Right colon	5 (22.7)
- Left colon	2 (9.1)
- Stomach	2 (9.1)
Multiple perforations per site, No. (%)	8 (36.4)
Re-GIP Features	
Prevalence, No. (%)	7 (31.2)
Time interval between LT and reperforation, median (IQR), d	32 (21.5-69.5)
Post-LT pre-GIP relaparotomy, No. (%)	2 (28.6)
Causes of relaparotomy, No. (%)	
Bleeding	1 (14.3)
Biliary leak	1 (14.3)
GIP during ICU stay, No. (%)	3 (42.9)
Enteral liquid in peritoneum, No. (%)	3 (42.9)
Multiple site of perforations, No. (%)	1 (14.3)
Sites of perforation	
Jejunum/ileum	4 (57.1)
Transverse colon	1 (14.3)
Right colon	2 (28.6)
Stomach	1 (14.3)
Multiple perforations per site, No. (%)	1 (14.3)
Surgical resection, No. (%)	5 (71.2)

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CMV, cytomegalovirus; GIP, gastrointestinal perforation; HCC, hepatocellular carcinoma; ICU, intensive care unit; IQR, interquartile range; IT, ischemia time; LOS, length of stay; LT, liver transplant; MELD, Model for End-Stage Liver Disease.

procedure for biliary atresia), serosal injury or devascularization of the bowel wall, prolonged LT procedure, long portal vein clamp time leading to gut congestion, retransplant, multiple transfusions, post-transplant intra-abdominal bleeding requiring reoperation, early portal vein thrombosis, high-dose steroid therapy, poor nutritional status, and cytomegalovirus (CMV) infection [1]. Data regarding adult patients are limited, and no histopathology analysis has been reported so far [1-3]. Graft-vs-host disease (GVHD) as well as recurrent or de novo inflammatory bowel disease (IBD) might be causative mechanisms that should be excluded as they are reported to be causes of enterocolitis in transplant patients presenting with diarrhea or GI bleeding [4,5]. The aim of the present study is to delineate the clinical presentation and outcomes of GIP post LT and to investigate possible clinical or operative risk factors and underlying pathogenic mechanisms on the basis of the histopathology and radiology examinations.

MATERIAL AND METHODS

This is a retrospective study based on a consecutive cohort of 361 first-time whole liver transplant patients at the Liver Transplant Unit of the University Hospital of Udine between January 2005 and December 2017. The demographic and clinical data were recorded from our hospital electronic database. Clinical characteristics of recipients and LT surgical details were analyzed as potential risk factors for GIP within the whole study cohort. All cases of GIP were investigated preoperatively with computed tomography (CT) scan. CT scan images at pre-LT evaluation and at GIT diagnosis were retrospectively reviewed by an expert radiologist in search of presence of any major risk factor or cause. All cases were submitted to relaparotomy. The extent of resection (either segmental resection and anastomosis or refreshing of the margins and closure) was

decided intraoperatively on the basis of the severity of peritoneal contamination, extent of the perforation, and viability of the affected bowel segment. The specimen was always sent for histopathology examination. At the retrospective review of the specimen by an expert GI pathologist, the targeted pathologies to rule out were CMV infection by immunochemistry analysis, GVHD, and IBD by morphologic analysis and antibody-mediated damage by C4D immunochemistry.

Categorical variables and frequencies were expressed by percentage, while continuous variables were expressed by mean (SD) or median (interquartile range [IQR]), as appropriate. Univariate logistic regression was used to explore predictive factors for GIP.

RESULTS

During the study period 22 patients developed at least 1 episode of GIP, with an overall incidence of 6.1%. The demographic and clinical data of the patients and details about GIP are reported in Table 1. The median pre-LT Model for End-Stage Liver Disease score was 17 (IQR, 13.25-23.25). A history of previous abdominal surgery was reported by 36.4% patients. At LT, the median time of portal clamping was 68.6 (SD, 20.4) minutes. The piggyback technique, with caval preservation, was used most frequently (77% of cases). An aortohepatic jump became necessary for reconstruction in 9.2% and Roux-en-Y choledochojejunostomy in 4.5% of cases. No iatrogenic GI injury was reported at LT. All the patients were under thromboprophylaxis with low-molecular-weight heparin or antiaggregant therapy with low-dose acetylsalicylic acid. The immunosuppression therapy was homogeneous among the patients, being based on calcineurin inhibitors and early steroid boost.

GIP developed at a median time of 18.5 (IQR, 12.5-28.5) days after LT and affected the jejunum and/or ileum in 63.6% of cases, transverse colon in 27.3%, right colon in 22.7%, left colon in 9.1%, and stomach in in 9.1%. A total of 27.3% of patients developed multiple sites of GIP. In 27.3% of cases the patient was already admitted in the intensive care unit when the complication occurred. At relaparotomy, in 68.2% of cases a diffuse fecal peritonitis was detected, and in 13.6% a biliary complication was associated. No association with hemorrhagic or macrovascular complications was detected. GIP recurred after effective surgical treatment of the index event in 31.2% of patients. Details about re-GIP are reported in Table 1. The 30-day mortality rate after relaparotomy was 40%.

The analysis of recipients' clinical characteristics (age, Model for End-Stage Liver Disease score, variceal bleeding episodes, portosystemic encephalopathy episodes, refractory ascites, history of previous abdominal surgery) and LT surgical details (operative time, portal clamping time, total ischemia time, type of outflow reconstruction, aortohepatic jump, Roux-en-Y choledochojejunostomy, number of packed red blood cells unit, milliliters of fresh frozen plasma, delayed laparotomy closure, relaparotomy before GIP or within postoperative day 30 in uncomplicated patients) as potential predictors of GIP identified history of previous surgery (odds ratio, 2.534; 95% CI, 1.004-6.395; $P = .046$) and relaparotomy (odds ratio, 2.652; 95% CI, 1.059-6.641; $P = .04$) as significant risk factors.

The retrospective review of pretransplant CT scan and CT scan at GIT diagnosis did not detect in any patients any sign of thromboembolic or steno-occlusive complication of any splanchnic vessel. Furthermore, the retrospective review of histopathology examination of the perforated GI segment resected at relaparotomy excluded any signs of CMV infection, GVHD, and IBD. In all the cases, including re-GIP, an ischemic necrosis with aspecific microangiopathy and microembolization were the pathologic features detected.

DISCUSSION

The recording of a higher prevalence of GIP in our clinical series compared with the data reported in literature [1] represented the rationale that motivated the present investigation and to our knowledge provided the largest single-center clinical series of GIP in adult liver recipients. Because of the overall low incidence of such complication, the available information about clinical features and possible underlying pathogenic mechanism are lacking in literature [1-3]. In the present study, the recipient-related risk factors of developing a GIP did not appear to be directly related to the severity of liver dysfunction and portal hypertension but rather to the adhesions caused by previous abdominal interventions. Furthermore, the negative effect of surgical trauma was verified even in the post-LT course as early relaparotomies resulted predictors of GIP. However, no iatrogenic vascular lesions were detected at CT scan nor were any of the factors associated with a complex LT procedure. Furthermore, the relatively high prevalence of multiple perforations at different GI segments and the significant rate of re-GIP after curative operation may indicate that a direct mechanical trauma could not be the main source of injury. Inflammation and transient hemodynamic instability may be implicated in the pathogenesis. Both the detection of ischemic necrosis with microembolization at the site of perforation and a 30% prevalence of patients developing a GIP when already admitted in the intensive care unit for other reasons may provide some indirect evidence.

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