European Radiology (2019) 29:3736–3745
https://doi.org/10.1007/s00330-018-5971-4

HEPATOBILIARY-PANCREAS

CT of acute rejection after liver transplantation: a matched case–control study

Jong Keon Jang[1] · Kyoung Won Kim[1] · Sang Hyun Choi[1] · So Yeong Jeong[1] · Ji Hun Kim[2] · Eun Sil Yu[2] · Jae Hyun Kwon[3] · Gi Won Song[3] · Sung Gyu Lee[3]

Received: 15 August 2018 / Revised: 4 December 2018 / Accepted: 13 December 2018 / Published online: 1 February 2019

Abstract

Purpose This study was conducted in order to investigate computed tomography (CT) findings associated with acute cellular rejection (ACR) following liver transplantation (LT) and their relevance to clinical outcomes.

Materials and methods We analyzed 120 patients with newly diagnosed ACR following LT for various liver diseases and 119 controls matched for age, sex, type of liver graft, and date of CT exam following LT. Two radiologists analyzed the images for morphological characteristics of the graft, morphological change in the major draining vein, graft enhancement in the portal venous phase, graft attenuation on noncontrast CT, and periportal halo. Univariate analysis was used to determine the association between radiological findings and ACR. Clinical outcomes, including treatment response and graft survival, were compared between patients with and without associated radiological findings.

Results Morphological characteristics of the graft (i.e., globular swelling), morphological change in the major draining vein (i.e., nonanastomotic luminal narrowing), and heterogeneous enhancement were significantly associated with ACR (all $p < 0.001$). On univariate analysis, the severity of morphological characteristics of the grafts (mild/severe: odds ratio [OR], 19.98/32.24) and morphological change in the major draining vein (without/with prestenotic dilatation: OR, 4.17/22.5) were significantly associated with the increased possibility of an ACR diagnosis. Clinical outcomes for treatment response and graft survival were not significantly different between patients with and without associated radiological findings.

Conclusions Globular swelling, nonanastomotic stenosis with or without prestenotic dilatation of the major draining vein, and heterogeneous enhancement of the graft on portal venous-phase CT were significantly associated with ACR.

Key Points

- *Globular swelling of the graft, nonanastomotic narrowing in the major vein, and heterogeneous graft enhancement on CT were significantly associated with acute cellular rejection (ACR).*
- *Associated CT findings were highly specific but not sensitive for differentiating ACRs from matched controls.*

Keywords Graft rejection · Liver transplantation · Computed tomography · Delayed graft function

✉ Kyoung Won Kim
kimkw@amc.seoul.kr

[1] Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea

[2] Department of Diagnostic Pathology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea

[3] Division of Liver Transplantation and Hepatobiliary Surgery, Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea

Abbreviations

ACR	Acute cellular rejection
CNI	Calcineurin inhibitors
CT	Computed tomography
DDLT	Deceased donor liver transplantation
HV	Hepatic vein
LDLT	Living donor liver transplantation
LT	Liver transplantation
RAI	Rejection activity index

Introduction

Acute cellular rejection (ACR) is a fairly common event following liver transplantation (LT), occurring in approximately 40% patients, with the incidence reaching 70% in studies based on protocol biopsy in the early postoperative period [1]. Most ACR events occur within the first year after LT and present with elevated bilirubin, transaminases, and alkaline phosphatase levels. Although milder forms of ACR can be managed without altering the immunosuppression regimen, moderate-to-severe ACRs and those not responding to immunosuppressive treatment can lead to prolonged liver dysfunction and chronic rejection, possibly resulting in graft loss and increased morbidity and mortality [2–5]. Therefore, early diagnosis and subsequent management of ACR are important to prevent unfavorable clinical outcomes. However, abnormal liver enzyme and bilirubin levels are not sensitive or specific for diagnosing ACR [6–8]; thus, liver biopsies are required to diagnose ACR in patients with clinical suspicion of rejection and to exclude other post-LT complications (infection, drug toxicity, and hemodynamic derangement). The histopathological diagnosis of ACR is based on the Banff classification, which is a grading system used to classify liver allograft rejection as absent, indeterminate, mild, moderate, or severe [9]. Nonetheless, liver biopsy is still significantly risky due to its invasiveness [10, 11].

Previous studies have investigated the feasibility of noninvasive tests, including blood tests and Doppler sonography, for discriminating ACR among LT recipients [12–15], and previous radiological studies have shown that decreased portal vein flow velocity and monotonous hepatic vein (HV) wave pattern on Doppler sonography suggests ACR after excluding other vascular or biliary complications. However, Doppler sonography has a wide range of sensitivity (53–92%) and specificity (48–89%) [12, 13, 15]. Given its high spatial and temporal resolutions, computed tomography (CT) is also commonly used in the postoperative period as a noninvasive modality to confirm or exclude vascular and biliary complications in recipients [16]. However, to our knowledge, no previous study has investigated the CT findings of ACR.

Therefore, this study investigated the CT findings associated with ACR and their relevance to clinical outcomes.

Materials and methods

This study was approved by our institutional review board, which waived the requirement for informed consent due to the retrospective nature.

Patients

Between January 2012 and June 2017, 2222 patients aged ≥ 18 years underwent LT in our institution for various liver diseases. During this period, a radiologist (J.K.J) retrospectively investigated pathological results of patients who underwent transjugular or percutaneous liver biopsy and retrieved data of 195 patients diagnosed with ACR. Forty-seven patients were excluded for absence of contrast-enhanced CT within 3 days of pathologic examination and 14 patients were excluded for presence of major vascular ($n = 8$) or biliary ($n = 6$) complications on postoperative surveillance CT or Doppler ultrasound (US). Additional 14 patients with coexisting liver diseases [i.e., hemodynamic derangement ($n = 9$) and recurrent viral hepatitis ($n = 5$)] based on pathologic examinations were excluded. The remaining 120 patients with availability of portal venous-phase contrast-enhanced CT images within 3 days of obtaining the pathologic examinations were finally analyzed as the ACR study group (Fig. 1).

The ACR group consisted of 85 males and 35 females (mean age, 52.4 ± 9.5 [mean ± SD] years); 41 patients (34.2%) underwent deceased donor LT (DDLT) using a whole liver graft and 79 underwent living donor LT (LDLT) using a right lobe (67 patients, 55.8%), left lobe (four patients, 3.3%), and dual (eight patients, 6.7%) graft. Hepatitis B cirrhosis (39 patients, 32.5%) was the most common indication for transplantation, followed by alcoholic (28 patients, 23.3%) and hepatitis C (20 patients, 16.7%) cirrhosis. The interval between LT and ACR diagnosis was 124.9 ± 239.1 days (mean ± SD; median, 28.5 days; range, 7–848 days; interquartile range, 12–118 days).

The study group patients were compared with control group patients selected from the same period and institution and matched for sex, age (± 2 years), type of liver graft (DDLT, LDLT with right lobe, left lobe, or dual grafts), and the postoperative day of conducting contrast-enhanced CT following LT (± 5 days). The control group included 119 patients because one female ACR patient with dual graft could not be matched. The most common indication for LT was hepatitis B cirrhosis (78 patients, 65.5%), followed by alcoholic cirrhosis (19 patients, 16.0%). Characteristics of patients of both groups are presented in Table 1.

Postoperative management and follow-up

After LT, patients were managed according to our institutional protocol as follows: The immunosuppression regimen included anti-interleukin-2 (basiliximab) induction, calcineurin inhibitors (CNIs; tacrolimus and cyclosporine), and corticosteroids. Mycophenolate mofetil was occasionally used in combination with a reduced dose of CNI.

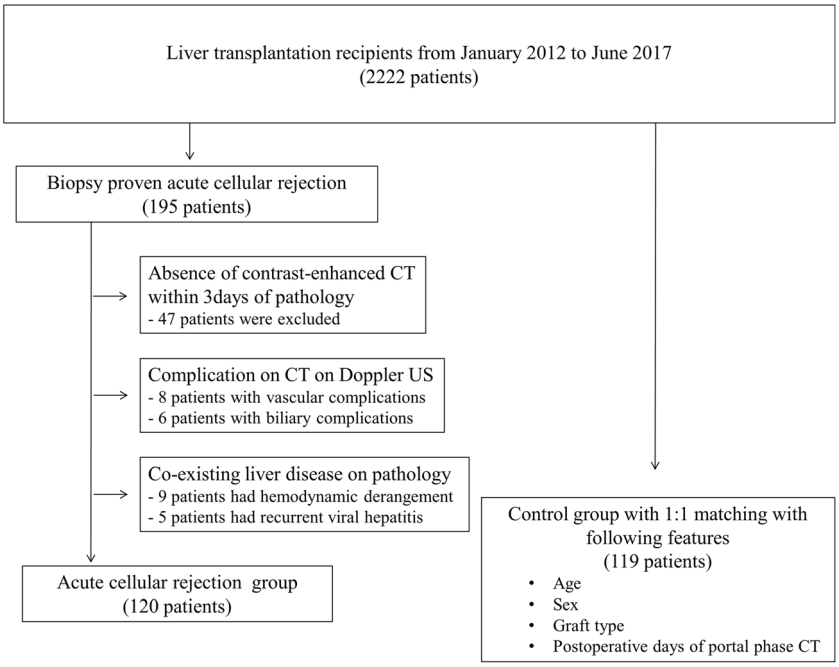

Fig. 1 Patient flow diagram

Corticosteroid was usually tapered off over 3 months following LT.

Only patients suspected as having ACR such as otherwise unexplained increased liver enzyme levels, no response to routine immunosuppressive treatment, or rebounding of liver enzyme level after normalization underwent transjugular or percutaneous liver biopsy. However, there was no defined criterion for performing liver biopsy, and decisions regarding whether patients should undergo liver biopsies were left to the clinicians' discretion. ACR was histologically diagnosed with RAI (rejection activity index) calculated as the sum of the scores for portal inflammation, bile duct inflammation and

Table 1 Patient characteristics

Characteristics	ACR ($n = 120$)	Non-ACR ($n = 119$)	p value
Age (years)	52.4 ± 9.5	52.28 ± 10.1	0.812
Sex			0.806
Male	85 (70.8%)	85 (71.4%)	
Female	35 (29.2%)	34 (28.6%)	
Indication for transplantation			0.01
Chronic hepatitis-associated cirrhosis (HBV and HCV)	59 (49.2%)	85 (71.4%)	
Alcoholic cirrhosis	28 (23.3%)	19 (16.0%)	
Biliary cirrhosis	3 (2.5%)	1 (0.8%)	
Cryptogenic cirrhosis	10 (8.3%)	6 (5.0%)	
Toxic hepatitis	12 (10%)	5 (4.2%)	
Acute hepatitis A	3 (2.5%)	0 (0%)	
Others*	5 (4.2%)	3 (2.5%)	
Type of graft			0.996
DDLT	41 (34.2%)	41 (34.5%)	
Right LDLT	67 (55.8%)	67 (56.3%)	
Left LDLT	4 (3.3%)	4 (3.4%)	
Dual LDLT	8 (6.7%)	7 (5.9%)	
Median interval between transplantation and CT (range)	27 (6–848) days	30 (6–852) days	0.802

Data are shown as the number of patients (%). The sum of percentage values may not be exactly 100% due to rounding up

ACR acute cellular rejection, *DDLT* deceased donor liver transplantation, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *LDLT* living donor liver transplantation, *CT* computed tomography

* Others include autoimmune hepatitis, cytomegalovirus infection, acute cellular rejection, polycystic liver and kidney disease, and Wilson disease

damage, and venous endothelial inflammation with involvement severity scored as 0–3, respectively, according to the Banff method. Patients diagnosed with ACR on biopsy were managed with an increased dose of immunosuppressive therapy. Those with severe ACR according to the Banff schema were typically treated with a bolus of high-dose steroids.

Our institution has an extensive radiological surveillance program for postoperative complications following LT including routine daily Doppler ultrasound for the first 7 postoperative days, routine contrast-enhanced CT within a week of transplantation, and an additional Doppler US or CT study if there was a clinical need during follow-up period.

During follow-up, clinical outcomes of patients with ACR were investigated using the electronic medical record. Patients were further grouped as good or poor responders according to their treatment response to immune suppression. Patients were defined as good responders if they recovered without the need for additional liver biopsy or when follow-up biopsy showed a decreased RAI, whereas patients were considered poor responders when follow-up biopsy demonstrated steroid-resistant ACR (i.e., no change or increased RAI), pathological analysis showed chronic rejection development, or they underwent retransplantation of the liver or liver-related death occurred due to intractable ACR. Graft failure was defined as retransplantation or liver-related death.

CT techniques

CT was performed using a 64- and 128-detector row CT scanner (Somatom Definition, Somatom Definition AS, and Somatom Definition Edge; Siemens Healthineers). CT images were obtained using the breath-hold technique at end-expiration at 120 kV and 200–220 mAs with automated dose modulation using the maximum allowable tube current. After acquiring unenhanced CT scans, intravenous contrast media, 150 mL iopromide (Ultravist 370; Schering AG), was administered at 3-mL/s flow rate using a mechanical injector (Percupump II; E-Z-Em, Inc.). Arterial phase images were acquired 15 s after the attenuation of the descending thoracic aorta reached 100 Hounsfield units; portal venous-phase images were obtained at 75 s following contrast media administration. Images were reconstructed with filtered back projection with 3 mm slice thickness.

Image analysis

In both the study and control groups, CT images were reviewed in consensus by two radiologists (K.W.K, with 15 years of experience in LT imaging; and J.K.J with 1 year of experience in LT imaging) who were blinded to group allocation and information in the pathology reports. The readers went through a training session in regard to morphological change of the graft with representative illustrations (Fig. 2). They analyzed the images on a picture archiving and communications system workstation in terms of morphological characteristics of the graft in axial plane, morphological change in the major draining vein, graft enhancement on portal venous phase, graft attenuation on noncontrast CT, and periportal halo. First, morphological characteristics of the graft were evaluated and classified into three categories: (a) normal, acute angles between all sets of graft margins; (b) mild globular swelling, mild rounded appearance of liver boarder leading to borderline obtuse angle between any one set of margins; or (c) severe globular swelling, apparently rounded appearance of liver boarder leading to obtuse angles between all sets of margins. Second, we categorized the morphological change in the major draining vein (right HV for DDLT or right LDLT; left HV for left LDLT) on axial portal venous phase as follows: (a) normal, (b) a short segmental nonanastomotic (> 2 cm distal to the anastomosis site) luminal narrowing of the HV without prestenotic dilatation, or (c) nonanastomotic narrowing of the HV with prestenotic dilatation (ratio of the diameters of the prestenotic and stenotic segments was > 2.0) [17]. Third, graft enhancement on portal venous phase was evaluated as follows [18]: (a) homogeneous enhancement; (b) segmental heterogeneous enhancement, < 50% of the graft surface area; or (c) diffuse heterogeneous enhancement, > 50% of the graft surface area. Fourth, on noncontrast CT, graft attenuation (high or iso-, low, and extremely low attenuation) compared with spleen and aortic blood attenuation was evaluated as reported in the previous study [19]. Fifth, decreased attenuation of the periportal area on portal venous phase was evaluated to determine the presence of a periportal halo. To avoid any recall bias, evaluation of each radiological finding was separated by an interval of 1 week, and the order of the cases was randomly changed for review.

Pathologic analysis

A radiologist (J.K.J) reviewed the clinical and histopathological reports of all biopsy specimens from 120 patients.

Median interval between transplantation and liver biopsy was 25.5 (range, 4–815) days. Initial RAI was 5.8 ± 1.9 (mean ± SD) and ranged from 3 to 9 in the ACR group. Mild (RAI 3–4), moderate (RAI 5–6), and severe ACR (RAI ≥ 7) were noted in 30 (25%), 41 (34.2%), and 49 (40.8%) patients, respectively. Of the 120 ACR patients, 64 (53.3%) underwent multiple biopsies (median number of liver biopsies per patient, 2.5; range, 2–5). Histopathological reports assessing RAI on follow-up biopsies were reviewed by J.K.J. Chronic rejection was identified by reviewing the histopathological reports of the explanted grafts or follow-up biopsy specimens.

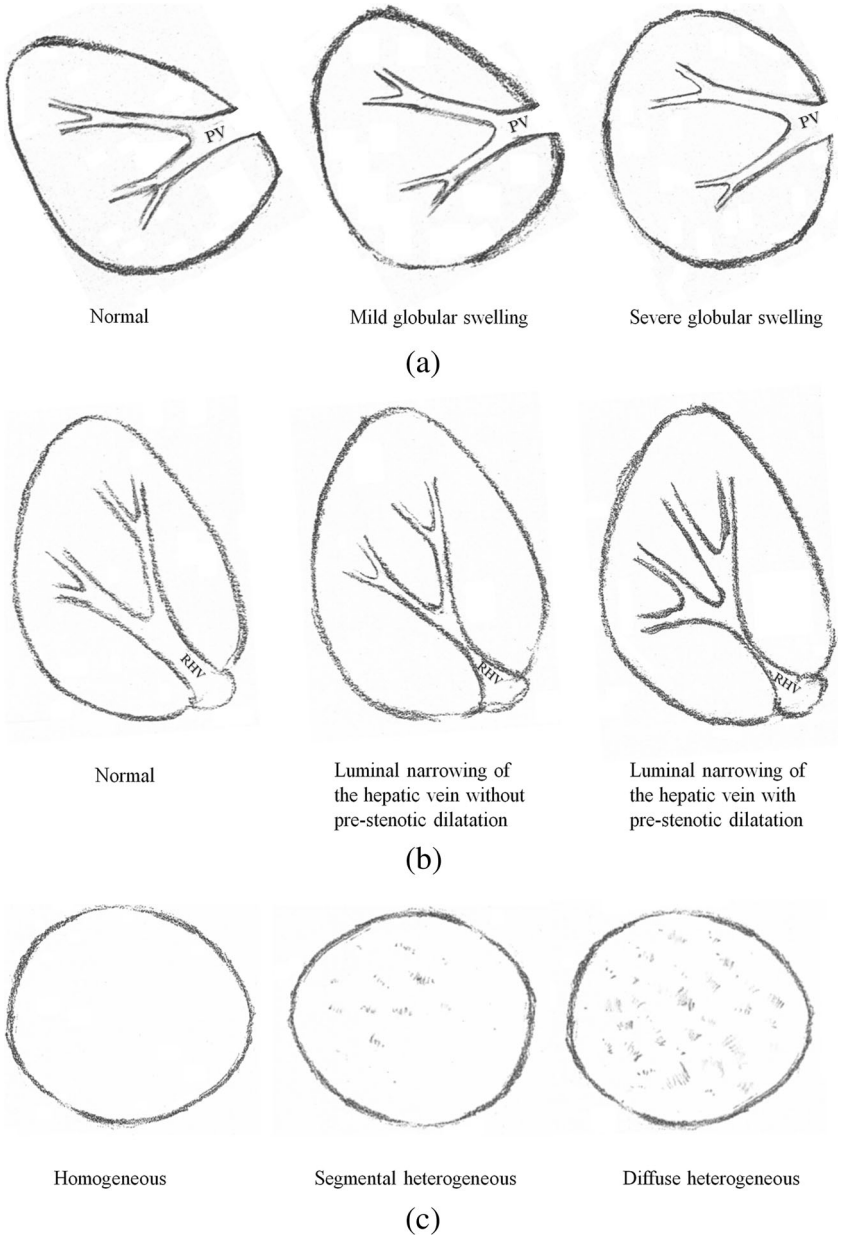

Fig. 2 Schematic illustrations of CT characteristics of the graft (e.g., right lobe graft). **a** Morphological characteristics. Normal: acute angles between all sets of graft margins; mild globular swelling: mild rounded appearance of liver boarder leading to borderline obtuse angle between any one set of margins; severe globular swelling: apparently rounded appearance of liver boarder leading to obtuse angles between all sets of margins. PV, portal vein. **b** Morphological change in the hepatic vein. RHV, right hepatic vein. **c** Graft enhancement on portal venous phase

Statistical analysis

The proportion of qualitative CT findings and patient characteristics were compared between the ACR and non-ACR groups using chi-square and Fisher exact tests. Mann–Whitney *U* test was used for continuous values. Univariate analysis was used to determine the association between radiological findings and ACR, followed by a diagnostic performance assessment. Collinearity and correlation between the qualitative CT findings were analyzed using Spearman correlation analysis. The ratios of the associative CT findings in good and poor responders were compared using Fisher exact tests. Graft survivals were assessed by Kaplan–Meier method and compared by log-rank test. IBM SPSS Statistics for Windows (version 21.0; IBM Corp.) was used for statistical analyses. Two-sided p values < 0.05 were considered statistically significant.

Results

The CT features of 120 grafts in the ACR patients and 119 grafts in the non-ACR patients are summarized in Table 2. Representative cases are illustrated in Fig. 3. Morphological characteristics of the grafts were significantly associated with ACR ($p < 0.001$). Although most grafts in the non-ACR group showed normal morphology, 31.7% (38/120) in the ACR group revealed globular swelling and 20% (24/120) showed severe

Table 2 CT features of the ACR and non-ACR groups

Image findings	ACR ($n = 120$)	Non-ACR ($n = 119$)	p value	Univariate logistic regression analysis	
				OR (95% CI)	p value
Morphological characteristics of the graft			< 0.001		
Normal	82 (68.3%)	117 (98.3%)		1	
Mild globular swelling	14 (11.7%)	1 (0.8%)		19.98 (2.58–154.91)	0.004
Severe globular swelling	24 (20.0%)	1 (0.8%)		32.24 (4.54–258.19)	0.001
Morphological change in the major draining vein			< 0.001		
Normal	92 (76.7%)	115 (96.6%)		1	
Short segmental nonanastomotic luminal narrowing without prestenotic dilatation	10 (8.3%)	3 (2.5%)		4.17 (1.11–15.58)	0.034
Short segmental nonanastomotic luminal narrowing with prestenotic dilatation	18 (15.0%)	1 (0.8%)		22.5 (2.95–171.70)	0.003
Graft enhancement on portal venous phase			< 0.001		< 0.001
Homogeneous enhancement	94 (78.3%)	116 (97.5%)		1	
Segmental heterogeneous enhancement (< 50%)	11 (9.2%)	3 (2.5%)		4.53 (1.23–16.69)	0.023
Diffuse heterogeneous enhancement (≥ 50%)	15 (12.5%)	0 (0%)			NS
Graft attenuation on noncontrast CT			0.086		NS
High or iso-attenuation	112 (93.3%)	116 (97.5%)			
Low attenuation	6 (5.0%)	3 (2.5%)			
Extremely low attenuation	2 (1.7%)	0 (0%)			
Periportal halo			0.096		NS
Presence	45 (37.5%)	30 (25.2%)			
Absence	75 (62.5%)	89 (74.8%)			

Data are shown as the number of cases (%). The sum of percentage values may not be exactly 100% due to rounding up

CT computed tomography, *ACR* acute cellular rejection, *CI* confidence interval, *OR* odds ratio, *NS* not significant

globular swelling. The globular swelling severity was significantly associated with the increased possibility of ACR (mild: odds ratio [OR], 19.98; severe: OR, 32.24) on univariate analysis. Sensitivity and specificity of the morphological characteristics of the grafts in the detection of ACR were 31.7% (95% CI, 23.5–40.8) and 98.3% (95% CI, 94.1–99.8), respectively.

Morphological change in the major draining vein (i.e., right HV for DDLT or right LDLT; left HV for left LDLT) was significantly associated with ACR ($p < 0.001$). Although most grafts in the non-ACR group showed no abnormal morphology in the major draining vein, 23.3% grafts (28/120) in the ACR group exhibited short segmental luminal narrowing in the major draining vein, and notably, 15% of the grafts in the ACR group (18 of 120) showed short segmental luminal narrowing with prestenotic dilatation in the major draining vein. On univariate analysis, short segmental nonanastomotic luminal narrowing in the major draining vein and prestenotic dilatation were significantly associated with a high probability of ACR (OR, 4.17 and 22.5, respectively). Sensitivity and specificity of morphological change in the major draining vein in the detection of ACR were 23.3% (95% CI, 16.1–31.9) and 96.6% (95% CI, 91.6–99.1), respectively. Most grafts in the non-ACR group showed homogeneous enhancement. However, 21.7% grafts (26/120) in the ACR group showed heterogeneous enhancement in the portal venous phase. Heterogeneous enhancement in the portal venous phase was significantly associated with ACR ($p < 0.001$). Sensitivity and specificity of graft enhancement in the detection of ACR were 21.7% (95% CI, 14.7–30.1) and 97.5% (95% CI, 92.8–99.5), respectively. If the graft has one or more of the three significant findings on CT, sensitivity and specificity of graft enhancement in the diagnosing ACR would be 39.2% (95% CI, 30.4–48.5) and 92.4% (95% CI, 86.1–96.5), respectively. Graft attenuation on noncontrast CT images and periportal halo were not meaningful radiological findings for detecting ACR. Radiological findings associated with ACR were significantly correlated with one another (Fig. 4). Morphological change of the graft was significantly correlated with morphological change in the major draining vein ($r = 0.707$, $p < 0.001$) and graft enhancement ($r = 0.501$, $p < 0.001$). In addition, morphological change in the major draining vein was significantly correlated with graft enhancement ($r = 0.545$, $p < 0.001$) (Table 3).

Of the 120 ACR patients, 55 (45.8%) were poor responders during follow-up. Median follow-up time for poor responders was 4 (range, 0–55) months. Overall, 16 patients (13.3%) had steroid-resistant ACR on follow-up biopsies, 18 (15%) were histopathologically diagnosed with chronic rejection, and 23 (19.2%) underwent retransplantation or died due to graft failure that was not otherwise specified. Two patients with steroid-

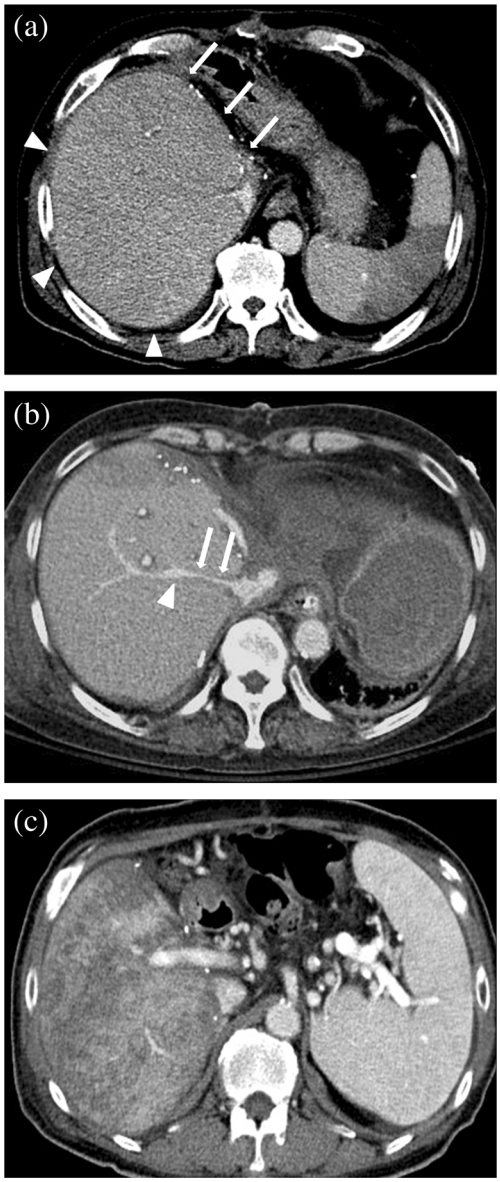

Fig. 3 Examples of computed tomography findings associated with acute cellular rejection. **a** A 59-year-old man underwent right lobe living donor liver transplantation (LDLT) for chronic hepatitis C. A portal venous-phase computed tomography (CT) axial image performed 35 days after liver transplantation (LT) showed severe globular swelling of the graft presenting obtuse angles between any sets of the graft margins including a resection margin (arrows) and free margins (arrowheads). Initial rejection activity index (RAI) was 9. **b** A 56-year-old woman underwent right lobe LDLT for alcoholic liver cirrhosis. A portal venous-phase CT axial image performed 4 days after LT showed short segmental nonanastomotic luminal narrowing of the right hepatic vein (arrows) with prestenotic dilatation (arrowhead). Initial RAI was 6. **c** A 65-year-old man underwent right lobe LDLT for alcoholic liver cirrhosis. A portal venous-phase CT axial image performed 72 days after LT showed diffuse heterogeneous enhancement and severe globular swelling of the graft. Initial RAI was 5

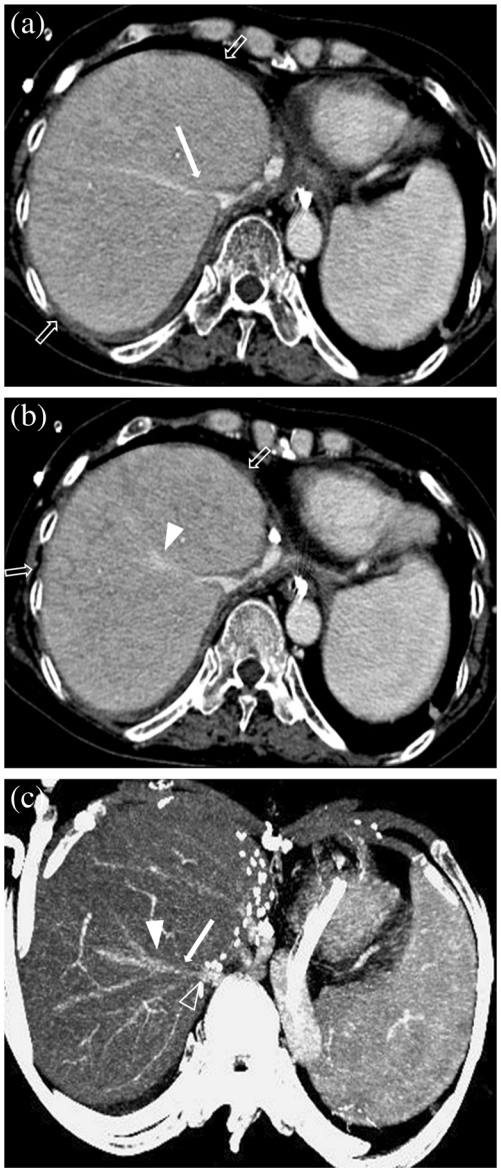

Fig. 4 Images from a 51-year-old woman (initial RAI 8) who underwent right lobe LDLT for primary biliary cirrhosis. On portal venous-phase CT axial images (**a**, **b**) performed 35 days after LT, liver graft showed severe globular swelling presenting obtuse angles between any sets of the graft margins (empty arrows), short segmental nonanastomotic luminal narrowing of the right hepatic vein (arrow) with prestenotic dilatation (arrowhead), and diffuse heterogeneous enhancement. **c** On axial maximum intensity projection (MIP) image, short segmental nonanastomotic luminal narrowing of the right hepatic vein (arrow) with prestenotic dilatation (arrowhead) was noted. Anastomosis between right hepatic vein and IVC was marked (empty arrowhead)

resistant ACR eventually developed chronic rejection. Among 16 patients with steroid-resistant ACR, three underwent retransplantation, two died of graft failure, and 11 received conservative management with steroid dose escalation. Of 18 patients diagnosed with chronic rejection, three underwent retransplantation, six died of graft failure, and nine were managed with immunosuppression escalation. Graft failure occurred in 36 patients, 15 of whom underwent retransplantation and 21 died. In total, 65 good responders had a median follow-up of 33 (range, 0–87) months. Of these, 47 patients (72.3%) did not require a subsequent biopsy after the initial biopsy and 18

Table 3 Correlation between radiologic findings associated with acute cellular rejection

		Morphological characteristics of the graft	Morphological change in t he major draining vein	Graft enhancement
Morphological characteristics of the graft	*p* value	–	< 0.001	< 0.001
	Correlation coefficient	1	0.707	0.501
Morphological change in the major draining vein	*p* value	< 0.001	–	< 0.001
	Correlation coefficient	0.707	1	0.545
Graft enhancement	*p* value	< 0.001	< 0.001	–
	Correlation coefficient	0.501	0.545	1

showed improvement in RAI on the subsequent biopsy. Grafts in the good responders showed slightly more globular swelling (36.9% [24/65] vs. 25.5% [14/55]), nonanastomotic luminal narrowing of the HV (26.2% [17/65] vs. 20.0% [11/55]), and heterogeneous enhancement on portal venous-phase CT images (26.2% [17/65] vs. 16.4% [9/55]) than those in poor responders, although these differences were not statistically significant (p = 0.237, 0.518, and 0.266, respectively) (Table 4).

Graft survivals between ACR patients with and without associated radiological findings (i.e., morphological characteristics, major draining vein, and graft enhancement pattern) were not significantly different (p = 0.948, 0.451, and 0.401, respectively) (Fig. 5).

Discussion

ACR occurs in 10–40% of LT recipients [20–22], although the incidence has decreased following the introduction of tacrolimus-based immunosuppression protocols. ACR diagnosis relies on histopathological analysis (Banff schema) because other liver tests are not sensitive or specific [14, 23]. Radiological studies including CT have played a limited role in ACR diagnosis. Although CT has been conventionally used to exclude other postoperative vascular or biliary complications, many CT findings have remained nonspecific and even overlap with those occurring in normal liver grafts. Therefore, it would be worthwhile to characterize the CT findings that favor or at least consistent with the diagnosis of ACR. To our knowledge, no study has addressed CT imaging findings of ACR.

In the present study, CT findings associated with ACR significantly increased the likelihood of diagnosis; these finding included abnormalities in morphological characteristics of the graft (mild and severe globular graft swelling), morphological change in the major draining vein (short segmental nonanastomotic luminal narrowing without prestenotic dilatation and with prestenotic dilatation), and graft enhancement pattern on portal venous phase. All significant findings correlated with one another (r = 0.501–0.707, all p < 0.001).

Tang et al [24] demonstrated a significant increase in the anteroposterior diameter of the grafts diagnosed with ACR on US, which is consistent with our study results. We assumed that the histopathological inflammatory feature of ACR involving portal inflammation, bile duct damage, and venous endothelial inflammation alters hepatic compliance and leads to graft swelling. Globular swelling of the graft might influence the nonanastomotic luminal narrowing of the HV and vice versa; this hypothesis corresponds with previous studies suggesting the association of ACR with veno-occlusive disease [25, 26]. Heterogeneous graft enhancement might be explained by the consequent hepatic congestion [17].

Although previous studies have reported that most ACRs improve with immunosuppression escalation and bolus steroid administration and generally have no adverse clinical outcomes [1, 27], in the current study, 45.8% ACR patients were poor responders and had a relatively high incidence of unfavorable clinical outcomes, which was due to a selection bias. Patients with mild and typical ACR could be excluded from this study because they responded well to conventional immunosuppressive treatment with no clinical need for liver biopsy. In this regard, in our study, median RAI was 5.8 at the initial biopsy in ACR patients,

Table 4 Clinical outcomes of patients with associated radiological findings

	Good responder (n = 65)	Poor responder (n = 55)	p value
Globular swelling (+)	36.9% (24)	25.5% (14)	0.237
Segmental nonanastomotic luminal narrowing of the major draining vein (+)	26.2% (17)	20.0% (11)	0.518
Heterogeneous enhancement (+)	26.2% (17)	16.4% (9)	0.266

Numbers in parentheses indicate numbers of patients. The sum of percentage values may not be exactly 100% due to rounding up

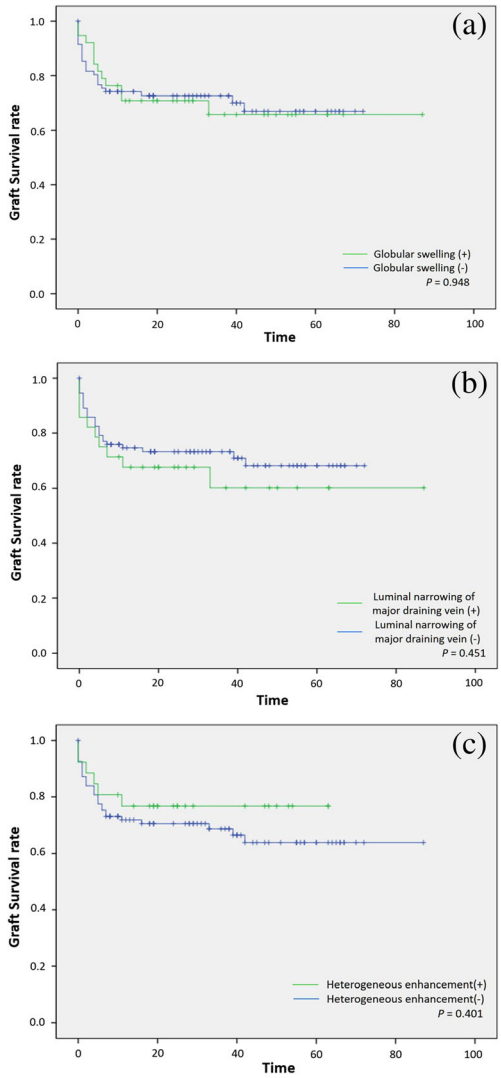

Fig. 5 Graft survival in acute cellular rejection patients. The Kaplan–Meier curves show no significant difference between patients with and without globular swelling of the graft (**a**), luminal narrowing of the major draining vein (**b**), and heterogeneous enhancement (**c**)

which is classified as moderate rejection according to the Banff schema, and 40.8% patients (49/120) showed severe rejection (RAI ≥ 7). Histologically documented severe ACRs frequently do not respond as frequently as mild ACRs to those treatments, leading to liver dysfunction and increased morbidity [4, 5].

Patients with associated radiological findings showed better treatment response, but the number of such patients was not significant. Of the 55 poor responders, 11 of 16 with steroid-resistant ACRs (68.8%) and nine of 16 with chronic rejections (56.3%) eventually responded to additional treatment, although it might increase morbidity due to side effects of using prolonged and intensive immunosuppression. Consequently, no significant difference was observed in graft survival between patients with and without associated radiological findings.

Given the noninvasiveness and high spatial and contrast resolution, MRI is increasingly performed in patients following the LT, particularly in patients with suspicious biliary complication, a major confounding factor of ACR [28]. Dynamic contrast-enhanced MRI may reveal more or less those same signs of the globular swelling, nonanastomotic stenosis with or without prestenotic dilatation of the major draining vein, and heterogeneous enhancement of the graft on portal venous phase. Moreover, using the hepatobiliary contrast agents, the degree of hepatocyte uptake of contrast agents and biliary excretion may be another important issue in patients with suspicious ACR. Therefore, further research would be required to evaluate the added value of the MRI, in predicting the ACR and the clinical outcomes.

This study has several limitations. First, due to the retrospective study design, a selection bias in the study populations, as described above, was possible. There was no defined criterion for performing liver biopsy, and decisions regarding whether patients should undergo liver biopsies were left to the clinicians' discretion. Nevertheless, patients with moderate or severe ACR in whom histological diagnosis was mandatory for clinical management constituted a relatively large proportion of our study population. Moreover, patients diagnosed with ACR but excluded from this study (47/195) due to the absence of portal venous-phase CT images obtained within three days after liver biopsy might have been relatively stable and thus did not attract the clinical attention to warrant an immediate scan. In this regard, the clinical and radiological features in the present study are more indicative of moderate-to-severe rejections (clinically worrisome ACR) than mild and typical ACR. A future prospective cohort study is warranted necessary to generalize these findings to the entire population of ACR patients. Second, intra- and interobserver variabilities in associated radiological findings remained a limitation, although consensus image analysis was performed by the two radiologists. We could not assess the positive/negative predictive value or accuracy of the associated radiological findings because this was a matched case–control study. Pathological correlations with these radiological findings were not performed. Third, we performed univariate analysis using only radiological findings for clinical outcome. Other factors that could affect clinical outcomes of previous studies included serum eosinophil and liver enzyme levels, ACR onset, and RAI level [14, 29]. Future prospective and randomized studies using all relevant factors to stratify clinical outcomes are needed.

In conclusion, globular swelling, nonanastomotic stenosis with or without prestenotic dilatation of the major draining vein, and heterogeneous enhancement of the graft on portal venous-phase CT were significantly associated with ACR and correlated with one another. These signs have high specificities although the sensitivities are low.

Funding This research was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT, and Future Planning (No. 2017R1E1A1A03070961).

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Kyoung Won Kim.

Conflict of interest The authors declare that they have no conflict of interest.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- case–control study
- performed at one institution

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