Case report

Upper urinary tract abnormalities in patients with late-onset hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: Computed tomography imaging characteristics

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Abstract

Purpose: To describe the imaging characteristics of the upper urinary tract (UUT) in addition to the bladder on computed tomography (CT) in adult patients with late-onset hemorrhagic cystitis (LOHC) after allogeneic hematopoietic stem cell transplantation (HSCT).

Subjects and methods: This retrospective study included 24 patients with LOHC who underwent urinary system CT between April 2006 and August 2013. UUT and bladder wall thickness and attenuation were measured before and after contrast material administration. Kidney density, collecting system dilatation, mucosal enhancement, submucosal edema, perivesical stranding around the UUT and bladder, and intravesical clots were evaluated. Diffuse and/or focal renal pelvis and ureter and bladder wall thickening were identified. Correlations between LOHC degree and UUT thickness, UUT attenuation, and uronephrosis were analyzed using Spearman's rank correlation coefficient.

Results: Diffuse and/or focal severe UUT and bladder wall thickening was observed in 22 patients (91.7%) with LOHC after HSCT. The median UUT and bladder wall thicknesses (interquartile range) were 2.5 mm (1.0–4.6 mm) and 4.8 mm (3.1–7.3 mm), respectively. Collecting system dilation (17; 70.8%), stranding surrounding the UUT and bladder (19; 79.2%), and intraluminal clots (two; 8.3%) were noted. Three patients underwent ureteral balloon dilation and D-J catheter implantation to resolve irreversible ureteral stenosis and uronephrosis. No significant positive correlation was seen between LOHC classification, UUT wall thickness or attenuation, or uronephrosis (P > 0.05).

Conclusion: UUT and bladder wall thickening and uronephrosis were observed on CT in patients with LOHC after allogeneic HSCT. Surgical treatment may be needed for irreversible ureteral stenosis.

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Keywords: Allogeneic hematopoietic stem cell transplantation; Late-onset hemorrhagic cystitis; Upper urinary tract; Computed tomography imaging

1. Introduction

Hemorrhagic cystitis (HC) is a common complication after allogeneic hematopoietic stem cell transplantation (HSCT) that results in prolonged hospitalization and occasionally death [1,2]. The reported incidence of HC varies widely (5–70%) because of discrepancies in definition criteria [3–5]. Early-onset HC occurs within 48–72 h of a conditioning regimen induced by the toxic effect of chemo-irradiation [6]. In comparison, late-onset HC (LOHC) occurs beyond 72 h after the preparative regimen and its pathogenesis has not been well elucidated [7]. As shown in prior studies, multiple potential etiologies including immunological mechanisms, graft-versus-host disease (GVHD), and viral infection may be associated with LOHC [4,8–10].

Because of patients' immunocompromised conditions, early imaging may be helpful after HSCT to define the extent of urinary tract disease and demonstrate complications. Patients with a diagnosis of LOHC would be referred for imaging if they did not respond to treatment and had atypical or severe symptoms [11,12]. In previous studies, bladder wall...
thickening with mucosal surface enhancement was seen on CT images in patients who had LOHC. In addition, intravesical clots and a sloughed uroepithelial lining was seen on CT imaging in some severe cases [13]. To our knowledge, however, no study has attempted to elucidate upper urinary tract (UUT) abnormalities (including those in the renal pelvis and ureter) using CT examinations in patients with LOHC after HSCT.

The aim of this study was proposed to identify the imaging characteristics on CT of the upper urinary tract in patients who were diagnosed with LOHC after allogeneic HSCT.

2. Materials and methods

2.1. Patients

Our institutional review board approved this retrospective study but waived the need for informed consent. Using a proprietary search engine developed by our imaging informatics department, an electronic search of medical record system database between April 2006 and August 2013 was performed to identify patients with a diagnosis of LOHC post-allogeneic hematopoietic stem cell transplantation (HSCT). Patients who underwent urinary system examination with or without a contrast CT examination were included in this study. Patients with bacterial, fungal, and tubercular urinary tract infections were excluded from this study based on history as well as physical examination and laboratory test results. The final cohort in this study consisted of 24 patients (13 women, 11 men; mean age, 26 years; range, 18–44 years). The median interval between LOHC onset and CT examination was 2.9 months (range, 1.5–9 months).

2.2. Clinical record

The clinical symptoms of patients with LOHC including hematuria, dysuria, abdominal pain, and urenephrosis were assessed and recorded. LOHC severity was graded and defined according to hemorrhage degree as follows: grade I, microscopic hematuria; grade II, macroscopic hematuria; grade III, macroscopic hematuria with clots; and grade IV, macroscopic hematuria that requires instrumentation for clot evacuation [15]. The diagnosis of acute GVHD was also recorded. The diagnosis of acute GVHD was also recorded.

2.3. CT technique

Urinary system CT examinations were performed using a multi-detector row CT scanner (Light Speed Volume CT; GE Healthcare, Milwaukee, WI, USA). CT images were obtained using the following parameters: 120 kV, 240–260 mAs, collimations of 64–0.6, slice thicknesses and increments of 5 mm, and sagittal and coronal reconstructions of 3 mm. Dynamic contrast-enhanced CT examinations were performed 60 s and 2–5 min after the intravenous administration of 80 mL of contrast material at a flow rate of 3 mL/s (iopromide 370 mg J/mL; Bayer Schering Pharma, Berlin, Germany).

According to our routine urinary system CT imaging protocol, all patients were asked to ingest 500–600 mL of water. A Foley catheter was clamped prior to the CT imaging acquisition to adequately distend the bladder. If the patient felt uncomfortable, the procedure was stopped.

2.4. Image analysis

Two radiologists (J.C. and Y.W.) with 10 and 17 years' experience in body imaging who were blinded to the medical records and other imaging studies reviewed the CT images to consensus.

The entire wall layers of the UUT and bladder were measured. Based on the modified Nicolet system, the UUT and bladder wall were classified as follows: none, imperceptible; grade 1, 1–2 mm; grade 2, 3–5 mm; and grade 3, >5 mm [15]. Abnormalities of the UUT and bladder wall distributed from the renal pelvis to the bladder were identified as diffuse thickening, while those of the UUT and bladder wall separated by normal-appearing sections were identified as focal thickening.

Mucosal stratification was distinguished by different CT attenuation values of the UUT and bladder wall layer resulting from infection-related pathophysiological changes. Attenuation of the UUT and bladder mucosa (uroepithelium) was measured and recorded before and after administration of contrast material using crosshair tools (pixel attenuation). Due to infection-related edema, muscularis propria can be distinct from mucosa, so this was evaluated and recorded.

Kidney parenchyma density was evaluated before and after contrast material administration. Collecting system dilation from the renal pelvis to the distal urinary tract was recorded. Intravesical clots were identified and recorded by higher attenuation values and good delineation from urine.

2.5. Statistical analysis

Urinary tract wall thickness and attenuation are reported as median values with interquartile ranges (IQR). The correlation between LOHC degree and UUT thickness and attenuation was analyzed by the nonparametric method of Spearman's rank correlation coefficient. The same statistical method was used to assess the relationship between LOHC degree and collecting system dilation. P values ≤ 0.05 were required in all tests to reject the null hypothesis. Statistical analyses were performed using MedCalc software (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Patient demographics

Patients' clinical data are shown in Table 1. All patients in this cohort had LOHC with urinary tract irritation after haploidentical HSCT (23/24; 95.8%) or identical allogeneic HSCT (1/24; 4.2%). The median interval between the
identification of LOHC and that of HSCT was 29 days (IQR, 9–120 days). All patients in this study had different degrees of hematuria as follows: four had grade I LOHC, 10 had grade II LOHC, six had grade III LOHC, and four had grade IV LOHC. CMV viremia was demonstrated in 21 patients (21/24; 87.5%). Acute GVHD was diagnosed in 21 patients (21/24; 87.5%) after allogeneic HSCT. Patients in this study presented with abdominal pain (20/24) and uronephrosis observed using ultrasonography (4/24) prior to the urinary system CT examination.

### 3.2. Imaging characteristics

Patients’ imaging characteristics are shown in Table 2. Diffuse thickening of the bladder wall was observed with a median thickness of 4.8 mm (IQR, 3.1–7.3 mm). Intravesical clots were observed in only 2 patients (2/24, 8.4%) with grade IV LOHC on CT images. The mucosal layer of the bladder wall clearly indicated with median attenuation of 52.5 (IQR, 40.0–60.0) and 100.0 HU (IQR, 90.8–140.0 HU) before and after contrast material administration in nine patients (9/9; 100%). Submucosal edema of the bladder wall was also seen in these nine patients (9/9; 100%) on CT images with contrast (Fig. 1). Perivesical stranding was observed in 19 patients (19/24; 79.2%).

Diffuse thickening of the UUT wall only was demonstrated in 22 patients (22/24; 91.7%). The median pelvic and ureter wall thickness was 2.5 mm (IQR, 1.0–4.6 mm; Figs. 2 and 3). According to the modified Nicolet system, grade 1 and 2 thickening of the renal pelvis and ureter wall was obtained in 10 and 12 patients, respectively, while no thickening of the renal pelvis and ureter wall was seen in two patients. Sixteen patients (16/24; 66.7%) had bilateral renal pelvis and ureter wall thickening, while six patients (6/24; 30.0%) had unilateral renal pelvis and ureter wall thickening.

Increased attenuation of UUT mucosal and submucosal edema was seen in five patients (5/9; 55.6%). Meanwhile, homogeneous enhancement of all layers of the pelvis and ureter walls was noted in four patients (4/9; 44.4%). The median intensity of the UUT wall was 45.0 (IQR, 39.0–48.8 HU) and 100.0 HU (IQR, 90.8–111.3 HU) before and after contrast material administration (Fig. 4), respectively. Stranding surrounding the UUT was seen in 19 patients (19/24; 79.2%), while a dilated collecting system was seen in 17 patients (17/24; 70.8%; Fig. 3).

### Table 1
Patients’ demographic data.

<table>
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<th>No.</th>
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<th>GVHD</th>
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**ALL** = acute lymphoid leukemia, **AML** = acute myeloid leukemia, **CML** = chronic myeloid leukemia.

**Table 2**
Imaging characteristics.

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<th>Characteristic</th>
<th>Bladder</th>
<th>Renal pelvis and ureter</th>
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<td>Wall thickness (median, interquartile range)</td>
<td>4.8 mm (3.1–7.3)</td>
<td>2.5 mm (1.0–4.6)</td>
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<td>Attenuation of urinary tract wall before contrast (median, interquartile range)</td>
<td>52.5 HU (40.0–60.0)</td>
<td>45.0 HU (39.0–48.8)</td>
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<tr>
<td>Attenuation of urinary tract wall after contrast (median, interquartile range)</td>
<td>100.0 HU (90.8–140.0)</td>
<td>100.0 HU (90.8–111.3)</td>
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<tr>
<td>Submucosal edema (n)</td>
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<td>5</td>
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<tr>
<td>Dilation of collecting system (n)</td>
<td>–</td>
<td>17</td>
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<tr>
<td>Surrounded stranding (n)</td>
<td>19</td>
<td>19</td>
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<tr>
<td>Intravesical clots (n)</td>
<td>2</td>
<td>0</td>
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</table>

Fig. 1. A 23-year-old female patient who had acute lymphoblastic leukemia presented HC 2 months after allogeneic HSCT. Diffuse thickening of the bladder wall (white arrow) with delineation of the inner layers (curved arrow) was shown on axial CECT. A large intravesical clot was detected on the CT images (empty arrow).
No abnormal attenuation of the kidney parenchyma was seen on CT images without contrast, whereas poor and heterogeneous enhancement was observed in three patients (3/9; 33.3%) on CT images after contrast material administration (Fig. 5).

No significant positive correlation was seen between LOHC degree and UUT wall thickening ($P > 0.05$) or UUT wall attenuation ($P > 0.05$) or between LOHC degree and collecting system dilation ($P > 0.05$).

Median follow-up time was 14.5 months (IQR, 3–60 months). Three patients (3/24; 12.5%) underwent ureter balloon dilation and D-J catheter implantation to resolve irreversible ureter stenosis and urenephrosis. No correlation was seen between urinary tract infection and overall survival outcomes. Five patients died of pulmonary infection and one patient died of cerebral infection.

4. Discussion

In this study, we demonstrated CT abnormalities of the UUT in addition to the bladder in patients with LOHC after HSCT. Diffuse thickening walls and dilation of the pelvis and
ureter were seen on the CT images. Mucosal hyperemia and submucosal edema of the UUT and bladder were seen as enhanced inner or all layers on CT images. Stranding surrounding the UUT as well as striated nephromas was also seen.

In general, ultrasound has been used to assess clots, thickening bladder wall, and urethral obstruction in patients with LOHC. CT is not routine examination for assessment of LOHC in clinical settings [13]. However, CT imaging demonstrated diffuse thickening wall and enhanced inner or all layer walls from bladder to renal pelvis in this study. In addition, the enhancement of mucosa and submucosa edema can be distinguished by using CT imaging after contrast. Similar to our results, the bladder changes in patients with LOHC were detected by using CT in prior publications as a common complication in patients after HSCT [13,16]. Schulze et al. reported the continuous thickening bladder wall in patients with polyomavirus hominis type 1 (BKV) LOHC after allogeneic HSCT on CT imaging. The detailed changes in wall of UUT and bladder could not be clearly detected only by using ultrasonography, especially when obvious urenephrosis did not present.

In addition, the mucosal enhancement related with hyperemia was also obtained after administration of contrast [13]. The LOHC was graded based on the severity of hematuria, which may associate with the inflammation of mucosa. According to the prior study, inflammatory hyperemia may be induced by the enhancement of mucosa after administration of contrast on CT imaging. We tried to measure the attenuation of urinary mucosa on CT imaging; however, the positive correlation with HC grade was not seen. It needed further study with larger sample size to clarify the relationship between inflammation of mucosa and grade of LOHC.

Urenephrosis is reportedly a complication of LOHC in severe cases of bladder clot obstruction [20,21]. In the study, only two patients had the clots in bladder. The major imaging abnormality of HC in this study was the wall thickening from bladder to renal pelvis that reflected the submucosa edema. A high proportion (17/24; 70.8%) of our patients presented with collecting system dilation on CT imaging that may associated with wall thickening of distal ureter and bladder. Moreover, three patients (3/24; 12.5%) underwent D-J catheter implantation to solve irreversable ureteral stenosis and urenephrosis obtained on the follow-up examination. UUT and bladder fibrosis and contracture in patients with LOHC may lead to lifelong sequelae [21]. The closely relationship between the thickening of UUT and irreversible ureteral stenosis was not demonstrated in this study involved such small sample size. The further study with larger sample size is needed to demonstrate the factor contributed to ureteral stenosis.

Tonolini et al. reported on the imaging features of acute pyeloureteritis caused by bacteria or fungus in HIV-positive patients. Subtly decreased parenchymal attenuation and mild-to-moderate pelvicalyceal or ureteral thickening was commonly observed in the nephrographic phase. In some cases, a thickening urinary tract was seen as the only perceptible feature of acute urinary tract infection [17]. Tuberculous infection with ureteral involvement also presented as ureteral wall thickening or distal ureteral strictures [18].

These non-specific imaging characteristics, including diffuse thickening of the UUT and bladder walls, mucosal hyperemia, submucosal edema, and collecting system dilation, might not be used as added clues for making a pathogenic diagnosis. In a clinic workshop, history, physical examination, and laboratory tests played major roles in the identification of pathogens in patients with immunocompromised conditions, especially after HSCT. BKV and CMV have been reported as independent risk factors of LOHC in patients after HSCT [1,4,15,19]. CMV seropositivity has been observed in up to 95% of adult donors and recipients because of the high prevalence of CMV infection in China [4]. As Xu et al. reported, CMV viremia was significantly associated with an increased incidence of LOHC based on univariate analysis [4]. In accordance with the earlier study, CMV viremia was confirmed in 21 patients (21/24; 87.5%) of this cohort. Acute GVHD, chemical toxins, immunological mechanisms, and radiation also contributed to LOHC development [19]. Even though the UUT abnormalities in patients with LOHC have not been reported, they might be induced by multiple potential etiologies similar to LOHC.

This study has some potential limitations. First, patients with symptoms such as abdominal pain and/or urenephrosis would be referred for CT examination although LOHC was a common complication in patients after HSCT. Accordingly, we may have missed some asymptomatic cases in this retrospective study. The second potential limitation was the lack of histopathological data from all patients with urinary tract disorders, which could not be obtained for obvious ethical reasons. As such, biopsy or surgical pathological validation is still needed in a further study to analyze the corresponding imaging characteristics.

In conclusion, wall thickening of the UUT in addition to the bladder as well as urenephrosis in patients with LOHC after allogeneic HSCT was observed on CT. These CT imaging findings can increase our awareness of possible irreversible ureteral stenosis and may help identify the need for further surgical treatment.

References


