Computed tomography imaging of acute gastrointestinal graft-versus-host disease after haematopoietic stem cell transplantation in children

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Aim of the study: To evaluate computed tomography (CT) findings of gastrointestinal graft-versus-host disease (GI-GVHD) occurring in children after haematopoietic stem-cell transplantation (HSCT).

Material and methods: From February 2013 to May 2018, 225 paediatric patients underwent HSCT. Sixty-eight patients (30%) presented with clinical diagnosis of acute GI-GVHD in the first 100 days after HSCT. Thirty-five (18 girls, 17 boys; age range, 2–18 years; mean age, 10.3 years) of 68 patients had abdominopelvic CT and included in study.

Results: Intestinal CT abnormalities were present in 33 (94%) and extra-intestinal CT findings were in 30 (86%) patients. Thickening of the bowel wall was the most common finding (31 patients, 89%), which involved the small bowel in 29 patients (83%), colon in 16 patients (46%), and both in 15 patients (43%). Oesophageal wall thickening was present in three patients (9%), and gastric wall thickening was in eight patients (23%). Bowel dilatation was detected in 13 patients (37%). Mucosal enhancement of the bowel wall was observed in 28 patients (80%). The prevalence of the extra-intestinal CT findings were: periportal oedema in nine (26%), ascites in 15 (43%), wall thickening and enhancement of gall bladder in 13 (37%), pericholecystic fluid in six (17%), hepatomegaly in 13 (37%), and splenomegaly in nine (26%) patients. One patient (3%) demonstrated free intraperitoneal air due to intestinal perforation.

Conclusions: CT is useful to support the clinical diagnosis of acute GVHD in children with GI symptoms after HSCT. Radiological evaluation is important because early diagnosis and treatment affect the prognosis of GI-GVHD.

Key words: computed tomography, gastrointestinal system, graft-versus-host disease, haematopoietic stem cell transplantation.

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Introduction

Haematopoietic stem-cell transplantation (HSCT) has been used progressively to cure haematopoietic disorders and haematological malignancies [1]. Graft-versus-host disease (GVHD) is one of the most serious complications, with an average incidence of 59% after HSCT. GVHD is an immunological disease that occurs due to the relation between T lymphocytes of the donor and epithelial cells of the recipient [2]. The skin, gastrointestinal (GI) tract, and liver are the most commonly involved organs [3]. GI-GVHD is one of the most common manifestations of acute GVHD, including abdominal pain, nausea, vomiting, abundant diarrhoea, fever, and weight loss [4]. The prognosis of acute GI-GVHD depends on immediate treatment with immunosuppressive treatment. Therefore, a rapid and accurate diagnosis is essential [3]. Although endoscopic biopsy is necessary for definitive diagnosis and staging of GI-GVHD, it may be contraindicated in patients with thrombocytopaenia and coagulopathy [5]. However, typical imaging features are present in the GI and hepatobiliary system. Awareness of these imaging findings is essential for early diagnosis and appropriate treatment to reduce morbidity and mortality of the GI-GVHD [2]. Abdominopelvic computed tomography (CT) is the primary imaging modality to determine abnormal findings in GI-GVHD [6]. The purpose of this study was to evaluate CT findings of GI-GVHD that occurred in children after HSCT.

Material and methods

From February 2013 to May 2018, 225 paediatric patients with different haemato-oncological diseases underwent HSCT in a single institution. Sixty-eight patients (30%) presented with clinical findings of acute GI-GVHD, including gastrointestinal symptoms like abdominal pain, nausea, vomiting, abundant diarrhoea, fever, intestinal bleeding, and weight loss in the first 100 days after HSCT. Biopsy was not performed in any of the patients because it was often contraindicated. All 68 patients were diagnosed and treated as acute GI-GVHD. Thirty-five of 68 patients had at least one abdominopelvic CT and participated in the study. Two (6%) of 35 patients underwent autologous and 33 patients (94%) had allogeneic transplantation. Twenty-two (67%) of 33 patients with allogeneic transplantation used HLA-match related donor (MRD), eight patients (24%) used HLA-match unrelated donor (MUD), and three patients (9%) used half-matched (haploidentical) donor. CT examinations were performed using dual source 64-slice CT scanner (Somatom Definition/AS 64×2: Siemens Medical Systems, Erlangen, Germany) with a slice thickness of 3 mm. All CT studies were performed after oral and intravenous (IV) contrast (1–1.5 ml/kg) administration. Scan-

ning was obtained 40–45 seconds after IV contrast injection for the maximum mucosal enhancement. CT exams were evaluated by a radiologist experienced in abdominal CT. Evaluated intestinal CT findings included wall thickening (defined as > 2 mm) and mucosal contrast enhancement of small bowel, colon, distal oesophagus, stomach, and also bowel dilatation. Involvement of small bowel was defined as segmental (duodenum, jejunum, ileum and terminal ileum) or diffuse. Involvement of colon was also described as segmental (cecum, ascending colon, transverse colon, sigmoid colon, and rectum) or diffuse. Extra-intestinal CT features were evaluated for the presence of periportal oedema, biliary abnormalities (wall thickening and wall enhancement of gall bladder, pericholecystic fluid), hepatomegaly, splenomegaly, ascites, and free air in the abdominal cavity. All CT findings were recorded.

Statistical methods

Statistical analyses were performed using SPSS statistic software, version 19.0 for Windows (IBM Company, Chicago, IL, USA). Associations of the CT findings with patient death and age were evaluated using Student *t*-test and χ^2 test. A *p*-value of < 0.05 was considered statistically significant.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from the patients for the study. The author declares no conflict of interest. This study received no financial support.

Results

This study included 35 patients (18 girls, 17 boys; age range, 2–18 years; mean age, 10.3 years) with various haemato-oncological diseases. Medical diagnoses leading to HSCT were: 11 patients (31%) with thalassemia, 10 patients (29%) with acute lymphoblastic leukaemia (ALL), six patients (17%) with acute myeloid leukaemia (AML), two patients (6%) with haemophagocytic syndrome, one patient (3%) with non-Hodgkin's lymphoma (NHL), one patient (3%) with Hodgkin's lymphoma (HL), one patient (3%) with Fanconi anemia (FA), one patient (3%) with sickle cell anaemia (SCA), one patient (3%) with osteopetrosis, and one patient (3%) with immunodeficiency. Table 1 shows the patients' characteristics. All patients demonstrated typical gastrointestinal findings of acute GI-GVHD. Diagnosis was confirmed with CT in all 35 patients (100%). Leukocyte (white blood cell) count showed low values in 19 patients and normal levels in 16 patients. Neutrophil count was in normal range in 20 patients, demonstrated high values in 13 patients, and was low in two patients at the time of CT. Microbiological profile was normal (no growth) in 29 patients, and four patients showed positive blood culture with *Enterococcus faecium*, *Staphylococcus epidermidis*, *Klebsiella*, and *Candida*, respectively. One patient demonstrated positive urine culture for *Candida albicans*, and one patient showed positive sputum culture for *Klebsiella* at the time of CT. Intestinal CT abnormalities were observed in 33 (94%) of the 35 patients, while extra-intestinal findings were present in 30 (86%). Thickening of the bowel wall was the most common finding emerging in 31 patients (89%). Wall thickening of the small bowel (Fig. 1B, 2A–B) was seen in 29 patients (83%) whereas involvement of the colon (Fig. 1A, 3B) was observed in 16 patients (46%). Wall thickening of both small bowel and colon was more frequent (15 patients, 43%) than the isolated involvement of the small bowel (13 patients, 37%) and colon (two patients, 6%). While segmental involvement was more frequently seen in the small bowel, diffuse involvement was observed more often in the colon. Bowel dilatation was present in 13 patients (37%). Small bowel dilatation was present in nine patients (26%), and colonic dilatation (Fig. 1A) was observed in 10 patients (29%). Six patients (17%) had dilatation of the both small bowel and colon. Oesophageal wall thickening was seen in three patients (9%), and gastric wall thickening was present in eight patients (23%). Bowel mucosal enhancement was identified in 28 patients (80%). Enhancement of the colon wall (Fig. 1A) was detected in 26 patients (74%), and small bowel mucosal enhancement (Fig. 1B) was present in 20 patients (57%). Prevalence of the extra-intestinal CT findings were: periportal oedema (Fig. 2A–B) in nine (26%), ascites (Fig. 3C) in 15 (43%), wall thickening and enhancement of gall bladder in 13 (37%), pericholecystic fluid (Fig. 3D) in six (17%), hepatomegaly in 13 (37%), and splenomegaly in nine (26%) patients. One patient (3%) demonstrated free intraperitoneal air with fluid collection (Fig. 3C) owing to intestinal perforation. One patient with GI-GVHD showed multiple splenic abscesses (Fig. 3A). Figure 4 shows the numbers and percentages of the intestinal and extra-intestinal CT findings. The mean interval between the time of HSCT and the time of CT exam was 41 days. With the mean follow-up period of 30 months (range 4–57 months), 12 patients (34%) had died from acute GI-GVHD and 23 patients (66%) were alive. In this study, different intestinal and extra-intestinal CT findings were not associated (p>0.05) with GI-GVHD-related death and patient age (Table 2).

Discussion

GVHD is the major reason of morbidity and mortality in patients with HSCT. In spite of the immunosuppressive

Table 1. Patient characteristics

Characteristics	Results
Age (years)	10.3 (2–18)
Sex (M : F)	17 : 18
Diagnosis	35
Thalassemia	11 (31%)
Acute lymphoblastic leukaemia	10 (29%)
Acute myeloid leukaemia	6 (17%)
Hemophagocytic S	2 (6%)
Non-Hodgkin's lymphoma Hodgkin's lymphoma Fanconi anaemia Sickle cell anaemia Immune deficiency Osteopetrosis	1 (3%)

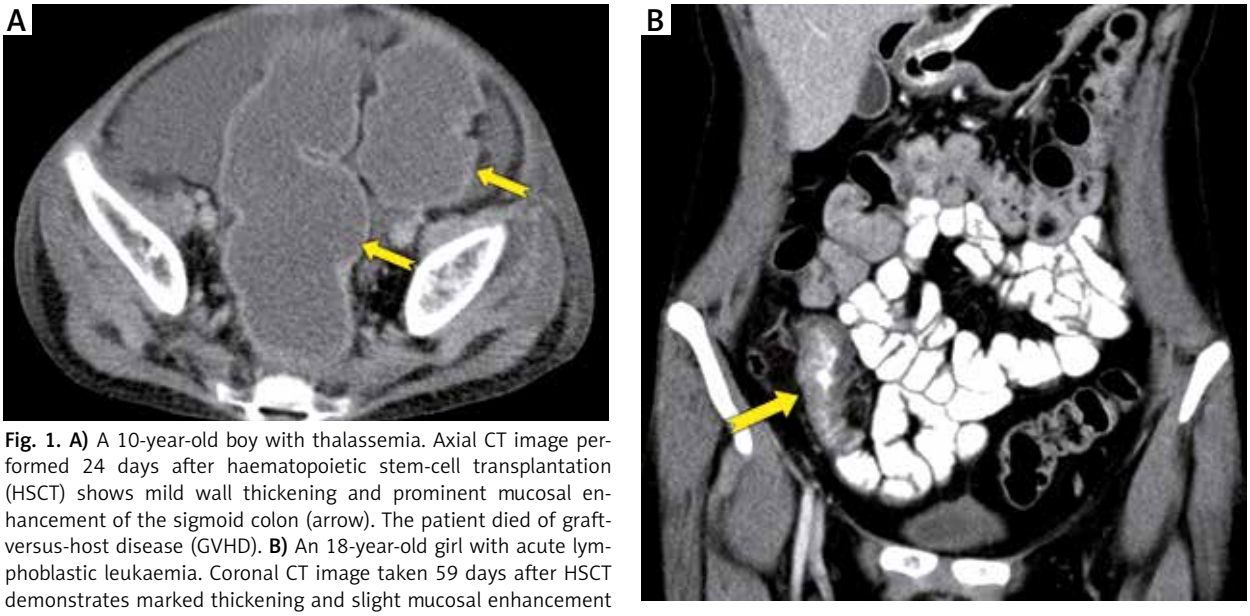

Fig. 1. A) A 10-year-old boy with thalassemia. Axial CT image performed 24 days after haematopoietic stem-cell transplantation (HSCT) shows mild wall thickening and prominent mucosal enhancement of the sigmoid colon (arrow). The patient died of graft-versus-host disease (GVHD). **B)** An 18-year-old girl with acute lymphoblastic leukaemia. Coronal CT image taken 59 days after HSCT demonstrates marked thickening and slight mucosal enhancement of the terminal ileum (arrow)

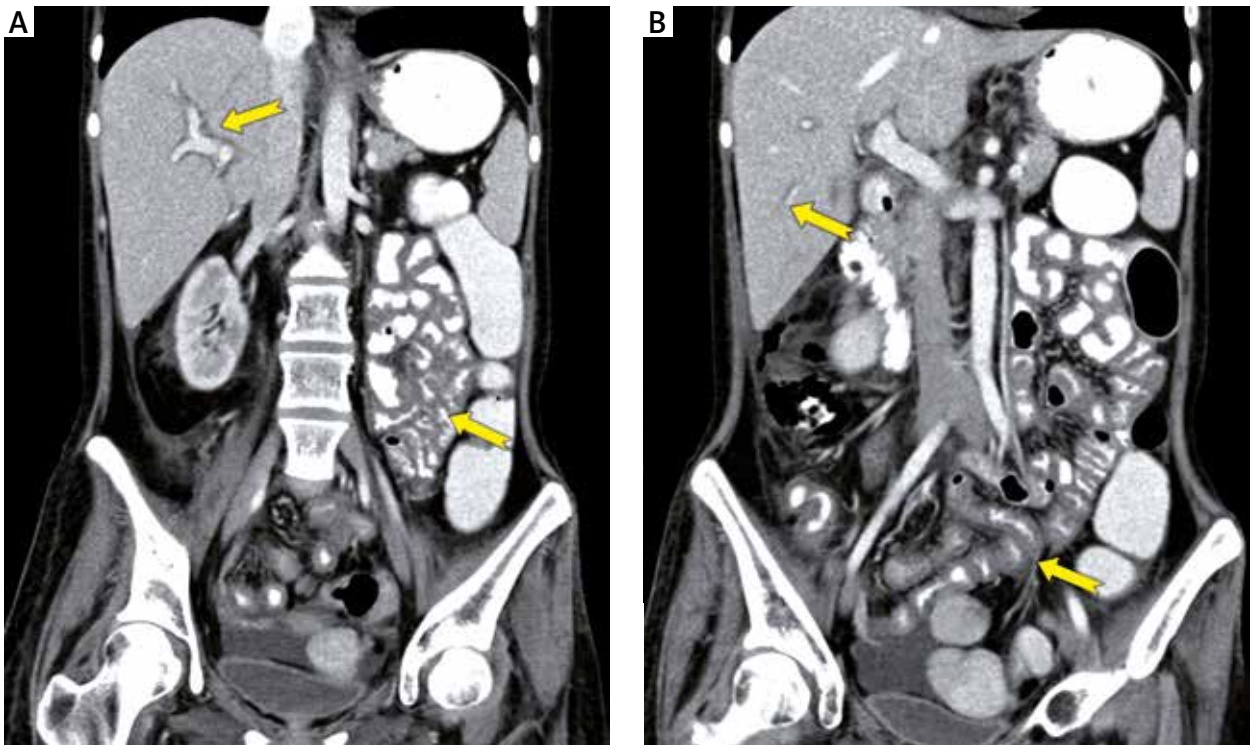

Fig. 2. A–B) A 16-year-old girl with acute lymphoblastic leukaemia. Coronal CT images performed 38 days after haematopoietic stem-cell transplantation reveal periportal oedema (upper arrows) and moderate wall thickening of the small bowel (lower arrows). The patient died of GVHD

prophylaxis, clinically significant acute GVHD develops in 15–50% of adults after HSCT [3]. In this study, acute GI-GVHD developed in 30% of the paediatric patients. Acute GVHD characteristically occurs 10–40 days after HSCT (generally < 100 days) whereas persistent or recurrent acute GVHD may appear after 100 days. The mean time between HSCT and CT exam was 41 days in this study. Skin is the first and most commonly (81%) involved organ, followed by GI tract (54%) and liver (50%). The lungs, genital tract, and joints are involved less commonly [2]. Nearly half of the patients with acute GVHD progress to chronic GVHD [7]. Chronic GVHD characteristically develops 100 days after HSCT. It is related with skin changes, hyperpigmentation, dry eyes and mouth, dysphagia, diarrhoea, hepatic fibrosis, and anorexia [2, 7]. To our knowledge, CT findings of acute GI-GVHD have been defined by several studies in adults; however, no recent series has been reported in children. In this study, intestinal CT findings were observed in

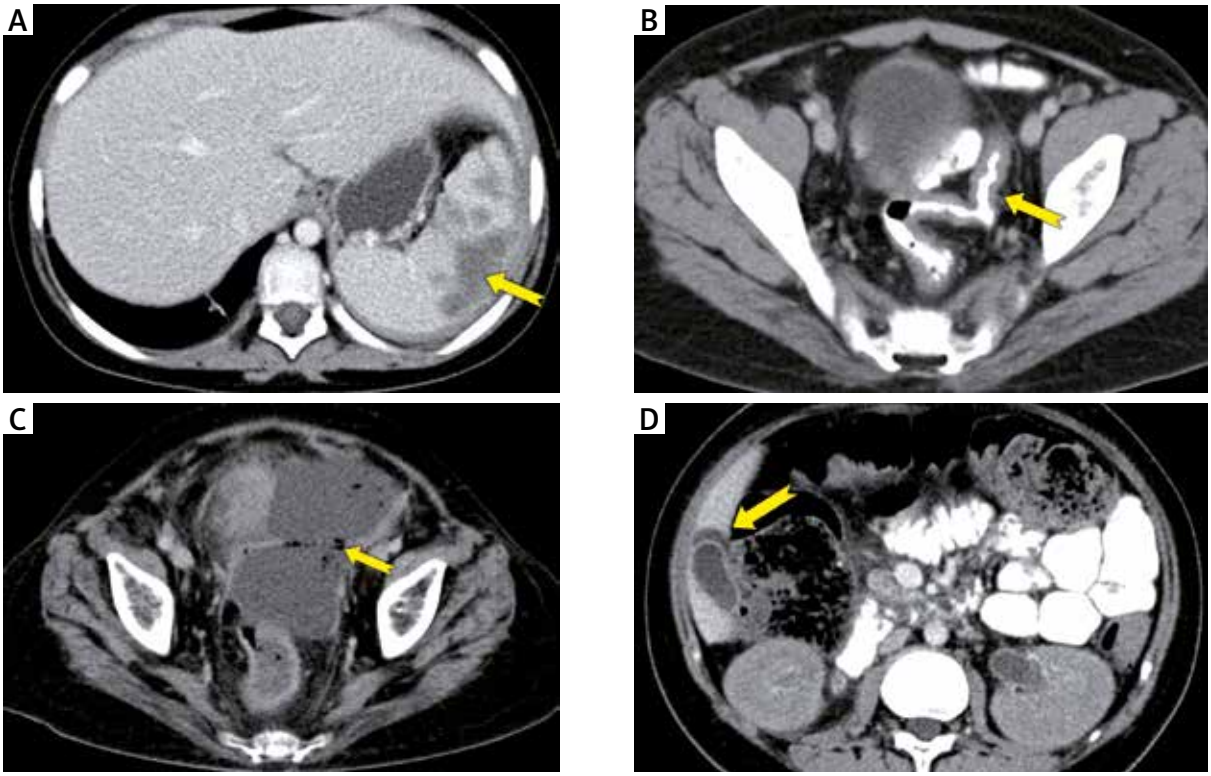

Fig. 3. A–B) A 14-year-old boy with acute myeloid leukaemia. **A)** Axial CT image taken 76 days after haematopoietic stem-cell transplantation shows multiple splenic abscesses (arrow). **B)** Axial CT image demonstrates moderate mucosal enhancement of the sigmoid colon (arrow). The patient died of GVHD. **C–D)** A 17-year-old girl with thalassemia. **C)** Axial CT image performed 47 days after haematopoietic stem-cell transplantation reveals free intraperitoneal air and fluid collection (arrow) due to intestinal perforation. **D)** Axial CT image shows wall thickening and enhancement of gall bladder with pericholecystic fluid (arrow). The patient died of GVHD

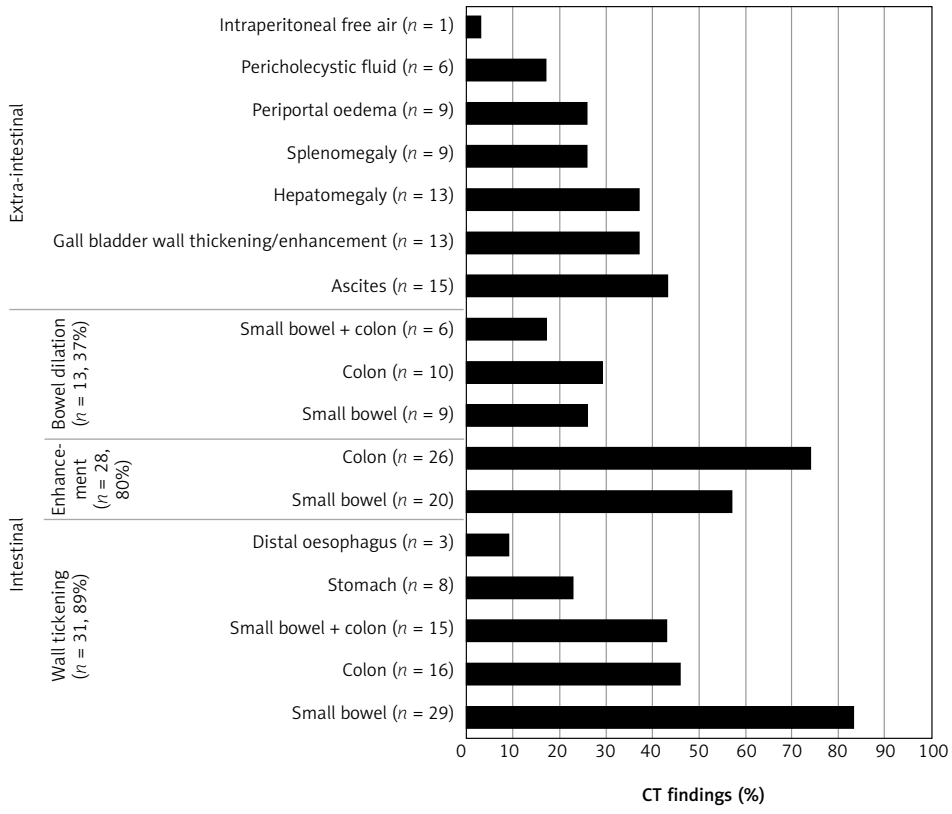

Fig. 4. Intestinal and extra-intestinal computed tomography findings (%) in patients with clinical diagnosis of acute gastrointestinal graft-versus-host disease (GI-GVHD)

Table 2. Correlation of intestinal and extra-intestinal computed tomography findings with acute gastrointestinal graft-versus-host disease-related death and patient age

Computed tomography findings		Alive, *n* (%)	Ex, *n* (%)	*p*	*n*	Age	*p*
Small bowel	–	5 (21.7)	1 (8.3)	0.294	6	11.67 ±4.41	0.451
	+	18 (78.3)	11 (91.7)		29	9.93 ±5.18	
Colon	–	13 (56.5)	5 (41.7)	0.404	18	9.78 ±5.10	0.594
	+	10 (43.5)	7 (58.3)		17/	10.71 ±5.04	
Distal oesophagus	–	22 (95.7)	10 (83.3)	0.231	32	10.41 ±4.88	0.504
	+	1 (4.3)	2 (16.7)		3	8.33 ±7.506	
Stomach	–	19 (82.6)	8 (66.7)	0.295	27	10.19 ±5.47	0.927
	+	4 (17.4)	4 (33.3)		8	10.38 ±3.50	
Periportal oedema	–	19 (82.6)	7 (58.3)	0.125	26	10.54 ±4.52	0.544
	+	4 (17.4)	5 (41.7)		9	9.33 ±6.56	
Gall bladder	–	14 (60.9)	8 (66.7)	0.735	22	8.86 ±4.76	0.075
	+	9 (39.1)	4 (33.3)		13	12.54 ±4.81	
Ascites	–	13 (56.5)	7 (58.3)	0.918	20	10.20 ±4.92	0.970
	+	10 (43.5)	5 (41.7)		15	10.27±5.38	
Hepatomegaly	–	13 (56.5)	9 (75)	0.275	22	11.23 ±5.11	0.129
	+	10 (43.5)	3 (25)		13	8.54 ±4.61	
Splenomegaly	–	14 (60.9)	12 (100)	0.065	26	10.31 ±5.16	0.308
	+	9 (39.1)	0 (0)		9	10.00 ±4.97	

94% and extra-intestinal CT abnormalities were detected in 86% of the patients with acute GI-GVHD, which is similar to the ratios of 95% and 83%, respectively, reported by Shimoni *et al.* [1]. In this study the prevalence of bowel wall thickening was 89%, which was the most common CT abnormality and was detected more frequently in the small bowel than in the colon. These results were consistent with previous reports [1, 3, 8], which described bowel wall thickening as a significant finding of acute GI-GVHD. The frequency of bowel dilatation was 37% in this study, which was compatible with some reports [1, 3]. However, Donnelly and Morris [6] found bowel dilatation in 94% of their paediatric patients, which was significantly higher than the rate seen in this study. They suggested that multiple fluid-filled dilated bowel loops were a characteristic CT finding in children with acute GI-GVHD. Also, Brodoefel *et al.* [8] reported the incidence of bowel dilatation as 94% in adults with GI-GVHD. In this study, the prevalence of bowel mucosal enhancement (80%) showed similar rates with the authors [6, 8] who reported significantly higher rates of bowel dilatation. However, Shimoni *et al.* [1] and Kalantari *et al.* [3] reported lower rates of a mucosal enhancement: 16% and as 54%, respectively. The prevalence of oesophageal wall thickening was 9% and gastric wall thickening was 23% in this study, which was close to the rates of previous reports [1, 3].

It should be considered that intestinal CT findings of GI-GVHD may also be demonstrated by neutropenic colitis (typhlitis), pseudomembranous colitis, drug or radiation related mucositis, and viral or fungal enterocolitis [9]. Differentiation of GI-GVHD from infectious enterocolitis is essential because GI-GVHD requires immunosuppressive treatment, which is contraindicated in infectious enterocolitis [3]. Neutropaenic colitis (typhlitis) mainly involves the cecum, ascending colon, and sometimes the ileum, in contrast to GVHD. It characteristically shows caecal wall thickening with inflammatory stranding on CT [9, 10]. GI-GVHD usually involves both the small bowel and colon, but the small bowel is more often involved [2], as seen in this study. Pseudomembranous colitis is related with broad-spectrum antibiotic therapy, which affects the intestinal flora and results in overgrowth of Clostridium difficile [9]. It usually manifests as pancolitis with marked wall thickening; small bowel involvement is uncommon [2]. Drug- or radiation-induced mucositis is known as mucosal barrier injury and leads to segmental or diffuse gastrointestinal tract involvement [9]. CMV colitis shows similar findings with typhlitis [9]. Intestinal wall thickening is typically moderate in acute GI-GVHD, whereas it is usually more severe in most cases of infectious enterocolitis. Bowel dilatation and abnormal mucosal enhancement are significantly more common in acute GI-GVHD than the different infectious enterocolitis [11]. Despite these imaging findings, clinical history, time and type of HSCT, laboratory values, and stool studies are crucial for a definitive diagnosis [2].

Regarding the extra-intestinal findings, ascites was the most common finding (43%) in this study. Calantari *et al.* [3] found engorgement of the vasa recta (91%) and stranding of mesenteric fat (73%) as the most common extraintestinal findings, which were not included in this study. They reported the prevalence of other extraintestinal findings with similar rates to those seen in this study. Brodoefel *et al.* [8] found the incidence of biliary abnormalities to be 74%, which was the most common extraintestinal finding in their study. Donnaly and Morris [6] reported a significantly high prevalence of gallbladder-biliary abnormalities in children and suggested acalculous cholecystitis as a life-threatening complication after HSCT. Ketelsen *et al.* [12] revealed that cholestasis and biliary sludge were

common findings and may manifest with temporary dilatation of the common bile duct.

This study had several limitations. It was a non-randomised retrospective study, it included a small number of patients, and depended on CT findings. Although all patients had a clinical diagnosis of GI-GVHD, it was not possible to compare their GI findings with a control group of other aetiologies. Biopsy was not performed in any of the patients because it was often contraindicated. Larger prospective studies may be needed to confirm the CT findings.

Conclusions

CT is useful to support the clinical diagnosis of acute GVHD in patients with GI symptoms after HSCT. Radiological evaluation is crucial because early diagnosis and treatment affect the prognosis of GI-GVHD.

The author declares no conflict of interest.

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