



Histologic diagnosis and grading of esophageal acute graft-versus-host disease

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Abstract

Acute intestinal graft-versus-host disease (GvHD) is a serious threat after allogeneic hematopoietic stem cell transplantation (alloHSCT). Although criteria for the histological diagnosis and grading of GvHD are well established for most parts of the gastrointestinal tract, evidence-based criteria have not yet been defined for the esophagus. Here, we evaluated esophageal biopsies obtained from 51 patients who underwent alloHSCT and compared the findings with those within the stomach and duodenum. In 32 of 51 biopsy samples of the esophagus, we identified a continuum of histological features of acute GvHD, ranging from vacuolar degeneration and single-cell apoptosis to the formation of clefts and mucosa denudation in advanced cases. These findings correlated with GvHD involving the stomach and duodenum and the clinical manifestations of GvHD in other organs. We therefore conclude that acute GvHD and esophageal GvHD can be diagnosed and graded histologically. Our findings may help to establish the histological diagnosis of acute GvHD using endoscopic biopsies from the esophagus and to explain the alterations observed in the esophageal mucosa in patients after alloHSCT.

Keywords Graft-versus-host disease · Esophagus · Stomach · Duodenum

Introduction

Intestinal graft-versus-host disease (GvHD) is an immune reaction of donor-derived immunocompetent cells targeting the intestinal system of the host. It occurs after allogeneic hematopoietic stem cell transplantation (alloHSCT) and results in cell and tissue destruction [16]. The clinical symptoms of intestinal GvHD include inappetence, nausea, pain, anorexia, diarrhea, and in more severe cases, protein-losing enteropathy, hypoalbuminemia, bloody diarrhea, and ileus [1], which can be life-threatening. Thus, intestinal GvHD causes up to 20% of deaths reported after alloHSCT [9].

Histopathology plays a pivotal role in the diagnosis and grading of acute intestinal GvHD throughout the various sites in the gut. Thus, the histological features of GvHD in the stomach as well as in the large and small intestine are well established [21]. However, reports concerning acute GvHD of the esophagus are rare, and most have focused on chronic changes including submucosal fibrosis [13, 22] or esophageal web [21], which may not be assessed in routine esophageal biopsies. Although signs of active GvHD in the esophagus (i.e., apoptosis of basal cells) were first mentioned several decades ago [13, 22], and there have been some subsequent reports of notable cases with acantholysis [14] or desquamation [17, 23, 24], the whole spectrum of histological findings in acute esophageal GvHD has not yet been assessed in an evidence-based grading system. Hence, criteria for diagnosing acute esophageal GvHD are not listed in the current NIH consensus [21].

In the present study, we evaluated biopsy samples of the distal esophagus after alloHSCT for signs of acute GvHD, performed grading, and validated the data by correlation to histological findings of GvHD in the stomach and duodenum as well as clinical features.

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Materials and methods

Using medical records from the Department of Pathology of the University Medical Center, Mainz, covering a period from 2002 to March 2018, we identified 65 sufficient biopsy samples of the esophagus (from the gastroesophageal junction), in a biopsy series comprising the gastric corpus and antrum, as well as the duodenum obtained after patients who had underwent alloHSCT. Of these cases, nine displayed signs of infection (four cases of esophageal candidiasis, three cases of herpes esophagitis, and one case each of *Helicobacter pylori* gastritis and cytomegalovirus gastritis [immunohistochemistry was performed in doubtful cases]), four showed signs of reflux or Barrett esophagitis, and one revealed signs of drug toxicity and were therefore excluded from the study. The remaining 51 biopsy series were included in this study, of which five patients did receive mycophenolate-mofetil (MMF) medication at the time of biopsy and seven others received MMF, which was ceased at least 1 month before biopsy. All patients were treated in the 3rd Medical Department of the University Medical Center, Mainz, and lifelong follow up was performed. GvHD assessment was conducted per clinical routine as recommended by the Glucksberg criteria; the clinical source data were reassessed according to the revised Glucksberg criteria [4] retrospectively. The characteristics of the patients are given in Table 1. The endoscopies and biopsies were performed in the first Medical Department of the University Medical Center, Mainz.

For each case, the original diagnostic slides were re-evaluated for signs of GvHD by one of the authors (A.K.). All biopsy samples were investigated using hematoxylin staining and periodic acid-Schiff staining. Biopsies from distal esophagus usually contained one or two specimens of squamous mucosa. Grading of GvHD on the basis of the squamous epithelium of the esophagus was performed analogous to the Lerner score for the skin GvHD (grade 0: normal epithelia; grade 1: cytoplasmic vacuolization; grade 2: single-cell apoptosis; grade 3: separation of the stroma-epithelial junction; grade 4: denudation) [5, 12]. The Lerner score was also used to grade GvHD in the stomach and duodenum (grade 0: normal epithelia; grade 1: single-cell apoptosis; grade 2: crypt or gland destruction; grade 3: focal epithelial loss; grade 4: diffuse epithelial loss, denudation) [5, 11]. Endoscopy reports were obtained from the clinical files and critically reviewed.

The AgreeStat2015.6 software (Advanced Analytics, LLC, Gaithersburg, MD, USA) on Microsoft Excel 2013 (Microsoft, Seattle, WA, USA) was used to perform Cohen's kappa analysis with linear weighting.

Table 1 Patient characteristics

Male/female	27/24
Age (years)	
Median	51
Range	19–69
Time since alloHSCT (days)	
Median	95
Range	22–1781
20–100 days	<i>n</i> = 28
100 days to 1 year	<i>n</i> = 17
> 1 year	<i>n</i> = 6
Disease	
AML	<i>n</i> = 28
MDS	<i>n</i> = 7
CMPN	<i>n</i> = 4
ALL	<i>n</i> = 3
Lymphoma	<i>n</i> = 7
Myeloma	<i>n</i> = 1
Aplastic Anemia	<i>n</i> = 1
Donor type*	
Sibling HLA identical	<i>n</i> = 5
Unrelated HLA identical	<i>n</i> = 36
Unrelated HLA different	<i>n</i> = 10

alloHSCT allogeneic hematopoietic stem cell transplantation, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *CMPN* chronic myeloproliferative neoplasm, *ALL* acute lymphoblastic leukemia

Results

Histology

Mucosal changes typical of acute GvHD were found in 32 of the 51 biopsy samples of the distal esophagus: 12 cases displayed focal vacuolization of the cytoplasm of the basal cells with marginalization of the nucleus (Fig. 1a). This feature is comparable to grade 1 acute GvHD of the Lerner classification regarding squamous epithelia of the skin. In 13 cases, apoptosis of individual cells of the basal or lower middle layer of the squamous epithelia together with mild spongiosis was identified, which is consistent with grade 2 GvHD (Fig. 1b, c). Both early- or low-grade lesions showed only slight increase in the number of inflammatory cells in the epithelial layer and stroma. Grade 3 type GvHD was identified in five cases on the basis of the formation of clefts or bullae on the junction of the epithelia and stroma while covered by stratified squamous epithelia (Fig. 1d). Mild inflammatory lymphatic cell infiltration was detected in the epithelia, more pronounced in the subepithelial stroma. Extensive destruction and loss of the epithelia were found in two cases that were therefore classified as grade 4 GvHD (Fig. 1e). The defect was

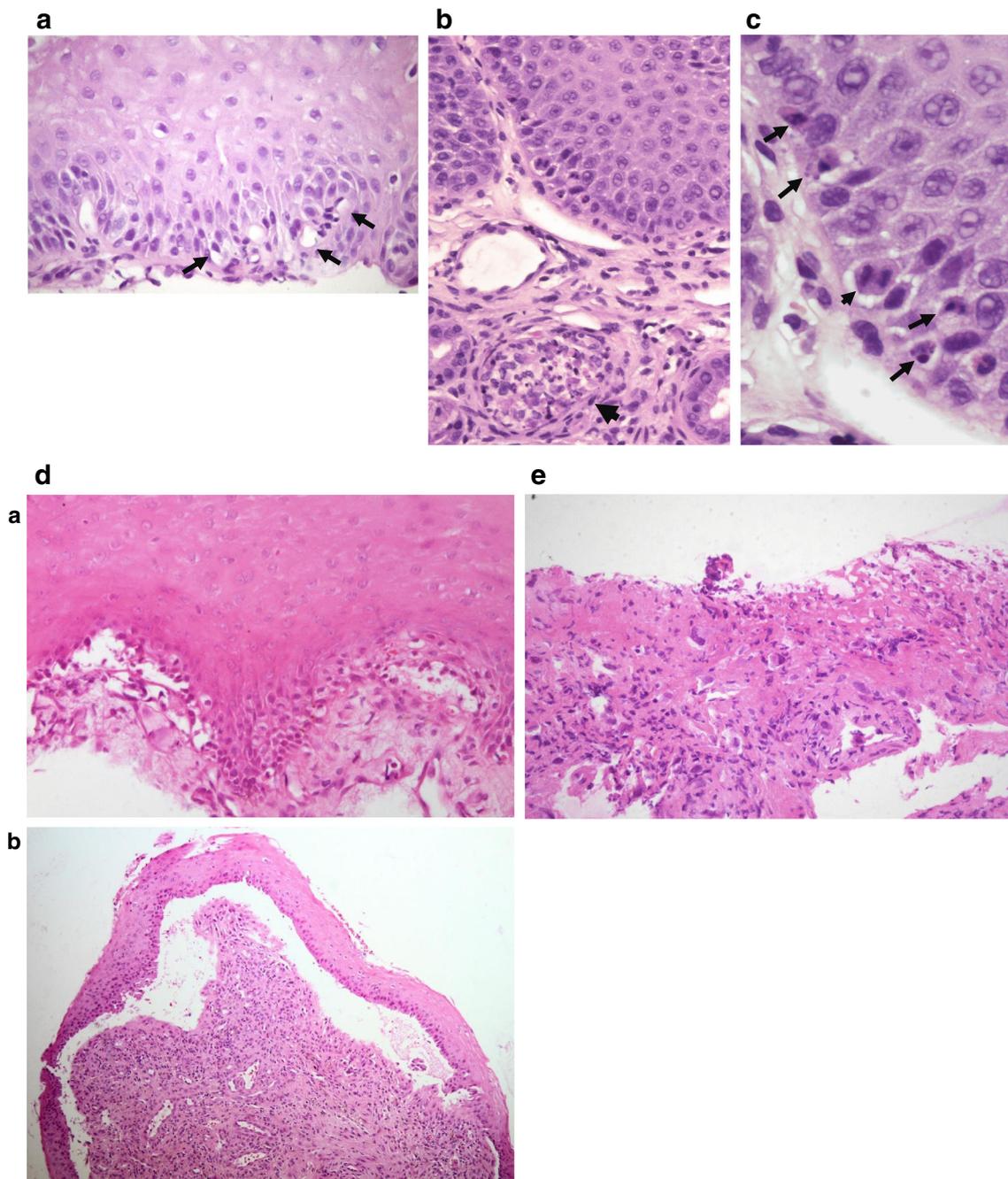


Fig. 1 Histological criteria for grading esophageal GvHD. **a** Grade 1 esophageal graft-versus-host disease: mild or early changes, characterized by vacuolar degeneration of the basal epithelial cells (arrows) (hematoxylin-eosin, $\times 63$). **b** Grade 2 esophageal graft-versus-host disease: moderate changes, characterized by single apoptotic bodies in the basal and suprabasal layer, with a neighboring gland destruction of the stomach (arrow) (hematoxylin-eosin, $\times 40$ (**a**), $\times 100$ (**c**, higher magnification of

b (arrows indicating apoptotic bodies, arrowhead mitosis)). **d** Grade 3 esophageal graft-versus-host disease: Severe changes, characterized by separation of the stroma-epithelial junction, resulting in the formation of clefts (**a**), which may cumulate to blistering (**b**) (hematoxylin-eosin, $\times 25$ (**a**) and $\times 5$ (**b**)). **e** Grade 4 esophageal graft-versus-host disease: severe, advanced changes, characterized by destruction of the epithelia and denudation of the stroma (hematoxylin-eosin, $\times 40$)

covered with fibrin and mild inflammatory cell infiltration. The remaining 19 biopsy samples of the esophagus revealed a normal histology with unaltered squamous epithelia and only a few lymphocytes in the underlying stroma.

In the stomach and duodenum, low-grade or early GvHD classified as Lerner grade 1 was identified and characterized by individual gland- or crypt cell apoptosis, which cumulated in cases of grade 2 GvHD to destruction

of the whole crypt or gland (Fig. 1b). In grade 3 cases, focal destruction, and in grade 4 cases, diffuse destruction of the surface epithelia were detected.

There was an association of the incidence and grade of GvHD of the esophagus with those observed in the stomach and duodenum (Fig. 2). Although most cases with no esophageal GvHD exhibited GvHD of the duodenum, only a few showed GvHD in the stomach, which were exclusively low grade. In grade 1 acute esophageal GvHD, all but one of the 12 patients revealed signs of GvHD within the stomach, mostly in the antrum, as well as the duodenum, some with higher histological grades. Esophageal GvHD of grade 2 and higher was also associated with increasing incidence and grades of gastral and duodenal GvHD. When comparing different sites, the association of acute esophageal GvHD was strongest with that of the antrum ($\kappa = 0.48$), followed by the corpus ($\kappa = 0.45$) and duodenum ($\kappa = 0.32$).

The highest incidence and severest grades of GvHD involved the duodenum, followed by the esophagus, antrum, and corpus. In all but one case of grade 1 esophageal

GvHD, GvHD was also detected histologically in the stomach and/or the duodenum. In 14 cases of GvHD of the stomach and/or duodenum, the esophagus was not involved.

Of the five patients under MMF, no changes in the esophageal mucosa was observed in two, while in the other three, the esophageal mucosa revealed apoptotic epithelial cells, equaling grade 2 GvHD, all of whom had epithelial cell apoptosis and/or gland destruction within the stomach and duodenum.

Endoscopic findings

In 10 of 19 patients without histological evidence of GvHD, normal esophageal mucosa was reported in one and in the rest minor signs of inflammation, mostly classified as gastro-esophageal reflux disease, were detected. Of the 12 cases of grade 1 esophageal GvHD, endoscopic imaging revealed mild inflammation in eight cases reminiscent of reflux or *Candida* infection. Only four cases of grade 1 esophageal GvHD showed no inflammation macroscopically. Of the 13 patients

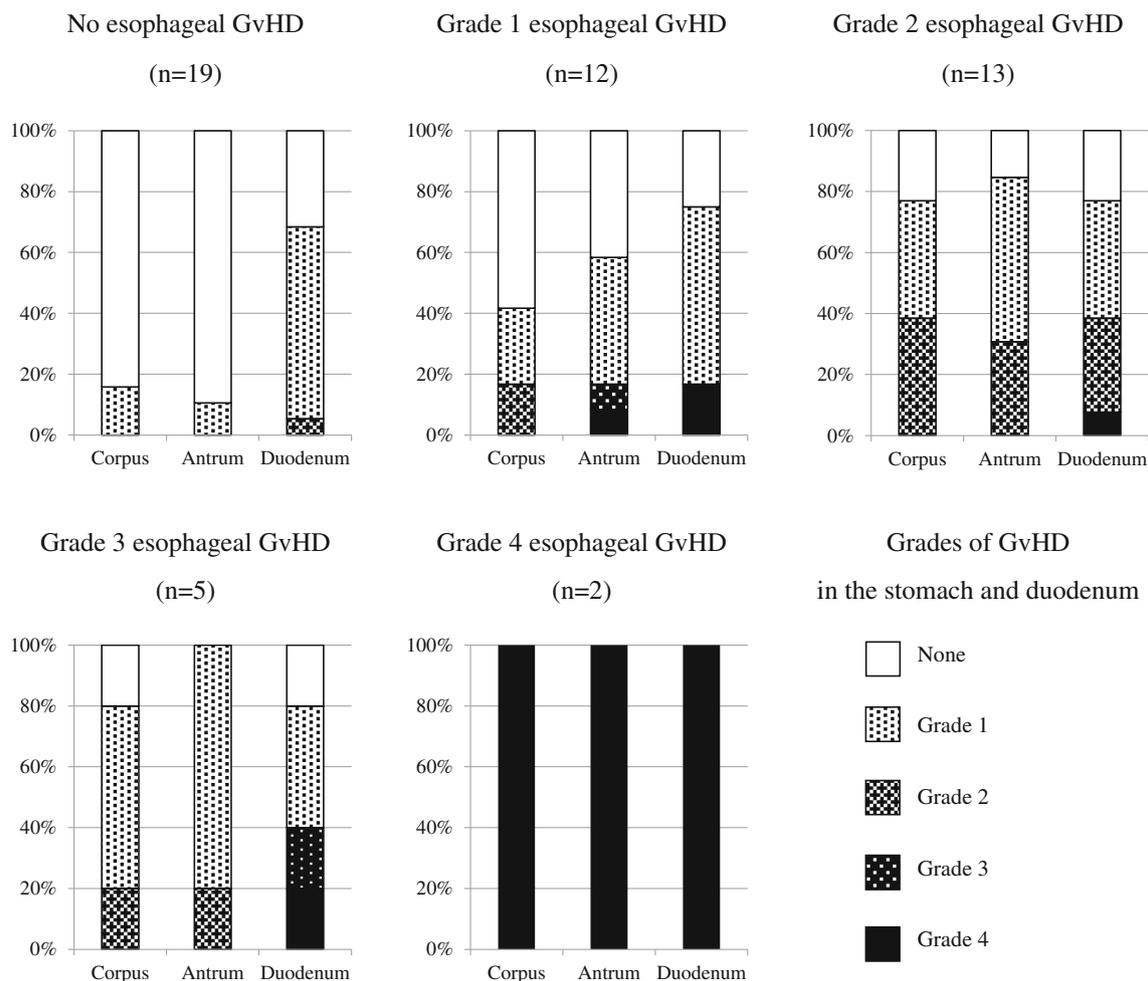


Fig. 2 Correlation of histological grades of esophageal graft-versus-host disease (GvHD) with the histological grades of GvHD in the stomach and duodenum

with grade 2 esophageal GvHD, 10 were reported to have erythema and erosions (Fig. 3a), while no visible lesions were detected in the remaining three patients. Five patients were reported to have grade 3 esophageal GvHD, of which three showed mucosal inflammation, and two had erosions. Two patients showed no signs of mucosal abnormalities. Moreover, in the two patients with grade 4 esophageal GvHD, endoscopy revealed scarring and ulcers (Fig. 3b).

Clinical findings

Of the 19 patients without histological signs of esophageal GvHD, 16 had abdominal discomfort ranging from inappetence to nausea, accompanied by emesis or diarrhea (including two patients treated with MMF) in three patients and weight loss in two. One patient had abdominal pain and two presented no abdominal symptoms (Table 2). Three patients had GvHD of the oral mucosa, two of the skin, one of the lower intestine, and one of the oral mucosa, skin, and lower intestine (who was treated with MMF) (Fig. 4; Table 3).

In the 12 patients with grade 1 esophageal GvHD, nausea or inappetence was reported in 7, of whom 2 had emesis and 1 had diarrhea. Four patients had diarrhea without nausea, and one did not present any intestinal symptoms. Other regions affected by GvHD were the skin in three patients, skin and lower gut in two patients, liver and oral mucosa in one patient, and the oral mucosa only in one patient.

Of the 13 patients with grade 2 esophageal GvHD, 7 presented with inappetence or nausea, 4 experienced additional diarrhea, and 2 had emesis. Two had abdominal pain, one of whom also had diarrhea. Two patients experienced diarrhea, with weight loss observed in one and no intestinal symptoms in the other. Other GvHD manifestations in these 13 patients occurred in the skin and lower gut in 4 patients (of which 2 were treated with MMF) and the skin only in 2 patients. One patient had GvHD of the oral mucosa, another of the oral

mucosa and liver (who was receiving MMF therapy), and two of the skin, liver, and lower gut, of whom one also had GvHD of the oral mucosa.

All seven patients with grade 3 or 4 esophageal GvHD suffered from nausea, emesis, and diarrhea. Of the five patients with grade 3 esophageal GvHD, three also had GvHD of the skin and lower gut, of whom one also had oral GvHD. One patient had GvHD of the oral mucosa and liver. Both patients with grade 4 esophageal GvHD also had GvHD of the skin, which in one was associated with GvHD of the oral mucosa.

Of the 19 patients without esophageal GVHD, four died from relapse of the primary disorder, one from sepsis, and one from bleeding. Of the 32 patients with esophageal GvHD, four died from infectious diseases, three from GvHD-related organ failure, two from relapse, and one each from renal and liver failure. The cause of death in one patient was not reported.

Discussion

In our study, we reported increasing grades of epithelial damage in the esophagus after alloHSCT, representing advancing grades of acute esophageal GvHD. Diagnosis and grading were validated by the correlation of histological findings in other sites of the upper gut, endoscopic findings, and clinical signs of GvHD. As part of this study, we have confirmed the striking histological resemblance of acute esophageal GvHD to acute dermal GvHD [7, 15].

According to the grading of acute dermal GvHD, vacuolar degeneration of the basal epithelial cells indicates early cell damage [5, 12]. Thus, this feature was included as grade 1 acute esophageal GvHD in our study. Most of those cases were endoscopically conspicuous, had clinical signs of acute GvHD, and nearly all were associated with acute GvHD of the stomach and duodenum, in contrast to those without

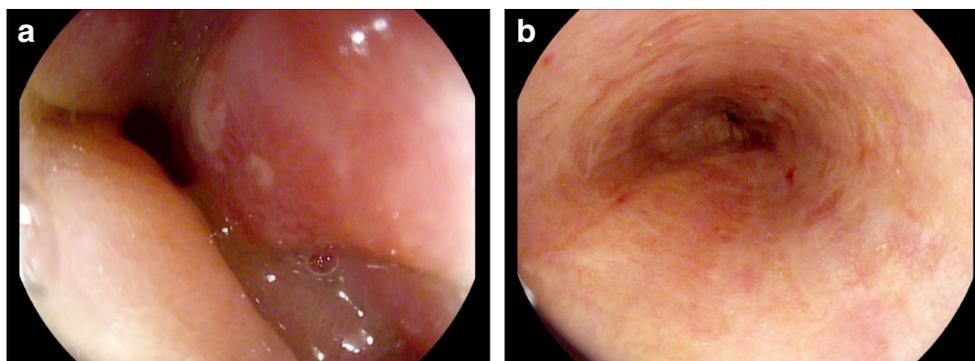


Fig. 3 **a** Endoscopic image showing mucosal erythema and small fibrinous erosions at the esophagogastric junction (histologically grade 2 acute esophageal graft-versus-host disease). **b** High-definition white-light endoscopy image showing marked erythema and absence of a

normal vascular pattern in the distal esophagus. In addition, mild scarring of the mucosa is seen (histologically grade 4 acute esophageal graft-versus-host disease)

Table 2 Esophageal GvHD compared with the overall Glucksberg score

Esophageal GvHD (Lerner)		Revised Glucksberg score (overall grade) in % (number of patients)					Chronic GvHD
Grade	<i>n</i>	0	1	2	3	4	
0	19	47 (9)		26 (5)	16 (3)		11 (2)
1	12	25 (3)		8 (1)	42 (5)	8 (1)	17 (2)
2	13	15 (2)		39 (5)	39 (5)	8 (1)	
3	5			20 (1)	40 (2)	40 (2)	
4	2				50 (1)	50 (1)	

GvHD graft-versus-host disease

histologically confirmed GvHD of the esophagus. Therefore, we may have verified vacuolar degeneration as an early- or low-grade sign of acute esophageal GvHD, in addition to the more advanced signs of apoptosis [8], acantholysis [14], and desquamation [17, 23, 24]. Using the Lerner classification of acute GvHD [5, 12], the findings within the stomach and duodenum could be graded using the same scheme, and compared with those of the esophagus. Increasing grades of esophageal GvHD were found to be associated with higher grades of gastric and duodenal GvHD, further verifying the applied grading system.

Generally, the histological features of acute GvHD in any organ are not entirely specific, especially in mild and very severe lesions [5]. The morphology may show some common features also seen in other inflammatory disorders of the

esophagus, such as reflux disease [25], in which cell vacuolization may be found [15]. However, in reflux disease, other classical signs like basal cell hyperplasia and elongation of the vascular papillae may be found, which along with the absence of GvHD signs in the stomach or duodenum may facilitate the separation from GvHD in most cases. Besides, immunosuppressive therapy with MMF is known to harm intestinal mucosa, including the esophageal mucosa. The most commonly reported feature of MMF toxicity in the esophagus is active esophagitis, with or without erosion and ulceration [10, 18, 20]. We did not observe any of these changes in the five patients receiving MMF. Some authors have also reported apoptotic damage of the esophageal squamous epithelial cells in patients treated with MMF [15, 18], which we observed in three patients receiving MMF. Since the features of GvHD in

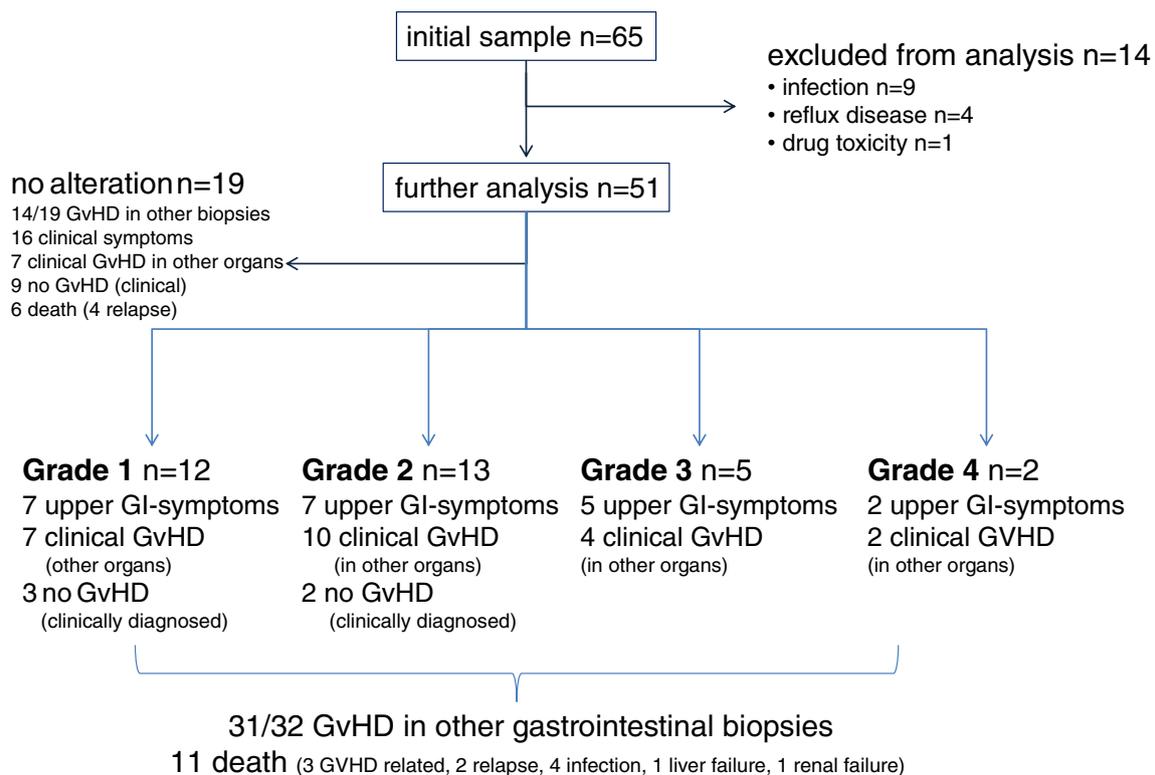
**Fig. 4** Clinical presentation of the patients with esophageal graft-versus-host disease

Table 3 Esophageal GvHD compared with the number of anatomical sites affected by GvHD other than the stomach or duodenum

Esophageal GvHD		Number of sites affected by GvHD other than the upper gut in % (number of patients)				
Grade	<i>n</i>	0	1	2	3	4
0	19	68 (13)	26 (5)		5 (1)	
1	12	50 (6)	33 (4)	17 (2)		
2	13	8 (1)	23 (3)	54 (7)	8 (1)	8 (1)
3	5	20 (1)		40 (2)	40 (2)	
4	2		50 (1)	50 (1)		

GvHD graft-versus-host disease

the stomach and duodenum were observed in these patients, the diagnosis of GvHD was more likely than MMF toxicity. However, information on immunosuppressive therapy should be sought, since MMF toxicity may result in histological features resembling active GvHD, in the esophagus as well as in other parts of the gut [20]. Cases that display characteristics of infectious diseases such as candidiasis and viral esophagitis were not included in our study, since after HSCT, infections, particularly viral and fungal infections, may lead to inflammatory changes in the mucosa that might end in ulceration, along with a low number of inflammatory cells in the lesion. These cases are differentiated from GvHD based on the isolation and identification of the infectious agent.

Previous studies on GvHD of different sites of the gut have included esophageal GvHD. In one study, apoptosis was considered as the criterion for histological diagnosis [2]. Based on this diagnostic criterion, their reported incidence of esophageal GvHD was 61%, compared to 89% in the antrum and 94% in the gastric corpus and duodenum. Two other papers have also reported esophageal GvHD, but without outlining their diagnostic criteria, where in one study, esophageal GvHD was observed in 3/21 biopsies of the esophagus only, with a higher incidence in stomach and duodenum (36/39 and 12/22 cases, respectively) [19], while the other reported esophageal GvHD in 3/13 patients, also with higher incidences of GvHD in the stomach and duodenum [6].

By including vacuolar degeneration as a diagnostic criterion for early- or low-grade GvHD and acantholysis and denudation as features of advanced GvHD, we observed that esophagus was a frequently involved site in cases of acute GvHD of the upper gastrointestinal tract (63%), second only to the duodenum (74%). In terms of the kappa values for grading, we found a moderate agreement [3] between the presence of GvHD based on esophageal findings and those of the stomach and the duodenum. Since we enrolled symptomatic (i.e., preselected) patients in our retrospective study, our findings reflect the relative incidence of GvHD in different biopsy sites among symptomatic patients, rather than the overall incidence of esophageal GvHD after alloHSCT.

The reason for the high expression of GvHD in the duodenum, as shown by our findings and previous studies, may be the

relatively abundant presence of immunocompetent cells in this area, which could support the inflammatory process in GvHD [16, 27]; the esophagus and stomach do not harbor as many immunocompetent cells as the duodenum. Pathophysiologically, in acute GvHD, the damage to the epithelial cells results from the interaction of donor T-cells with host cells, due to disparities of the minor histocompatibility antigens expressed by the host [26, 27]. Usually, the Fas/Fas ligand, perforin/granzyme, or TNF/TNF receptor trail induces the damage to host cells. In stratified squamous epithelia, the donor T-cells migrate from the systemic circulation through the connective tissue and basement membrane to the basal epithelial cells. Thus, the basal epithelial cells were the most severely damaged by the donor T-cells. This mechanism could explain the vacuolization and apoptosis, as well as the formation of clefts and bullae that occur predominantly in the lowest epithelial layer in cases of esophageal GvHD. Further, the basal cells represent the regenerating component of the epithelium, which has long been known to be most prone to GvHD [22].

Our findings of acute esophageal GvHD are in line with clinical findings of acute GvHD of the squamous epithelia in the skin, which was detected in 18 of the 32 patients with esophageal GvHD. However, GvHD of the squamous oral mucosa was reported in only seven cases with coexistent esophageal GvHD. Reports of GvHD of the lower gut in nine cases emphasize its extension throughout the intestine. The liver was reported to be involved in six cases. Patients with higher grades of esophageal GvHD were more likely to have manifestations of GvHD in various other organs.

In conclusion, acute esophageal GvHD can be diagnosed and graded with similar histological criteria as those applicable for skin GvHD. The first histological sign of esophageal GvHD may be vacuolar degeneration of basal cells. The incidence of GvHD in the esophagus is lower than that in the duodenum but higher than that in the stomach. The finding of esophageal GvHD may be of use in establishing the histological diagnosis and grade of acute GvHD. Involvement of the esophagus is associated with the manifestation of acute GvHD in the upper gut and other organs, especially the skin. Endoscopic features of inflammation of the esophageal mucosa are typical of esophageal GvHD.

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Author's contributions All the authors made substantial contributions to the acquisition, analysis, and interpretation of the data and drafting (AK: design, histology. HN and DvB: endoscopy. E.M.W.-D.: clinics). All the authors gave final approval for publication.

Compliance with ethical standards

This study was approved by the ethical committee of the medical board of Rhineland Palatinate (No. 0837.271.12 (8372)).

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

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