



Prospective evaluation for upper gastrointestinal tract acute graft-versus-host disease after hematopoietic stem cell transplantation

M Wakui, S Okamoto, A Ishida, H Kobayashi, R Watanabe, T Yajima, Y Iwao, T Hisamatsu, T Hibi and Y Ikeda

Keio BMT Program, Division of Hematology and Gastroenterology, Keio University School of Medicine, Tokyo, Japan

Summary:

The incidence and clinical significance of upper gastrointestinal tract acute graft-versus-host disease (upper GI GVHD) were prospectively evaluated in 44 Japanese patients who underwent allogeneic ($n = 26$) or autologous ($n = 18$) stem cell transplantation. Endoscopic examination was routinely performed between days 20 and 50 post-transplant and when symptoms of upper GI and/or acute GVHD of other organs were present. The results were compared with the historical records of 49 allograft and 20 autograft recipients. The diagnosis of upper GI GVHD was confirmed by histologic findings of GVHD and persistent upper GI tract symptoms. The incidence of upper GI GVHD was 46% in the prospective allograft group, higher than in the retrospective group. Upper GI GVHD was not diagnosed in any autograft patients. Twelve of 19 patients with upper GI GVHD had skin GVHD, and two of the 12 had concurrent lower GI GVHD. Upper GI GVHD was successfully treated with steroids and did not progress to symptomatic lower GI GVHD. In addition, upper GI GVHD completely resolved without specific alteration in immunosuppressant therapy in six patients. No risk factors for upper GI GVHD could be identified. The presence of upper GI GVHD did not significantly affect early death rate, incidence of chronic GVHD, and overall survival. In conclusion, by the prospective evaluation of the upper GI tract by endoscopy we could accurately diagnose upper GI GVHD in half our allogeneic recipients. However, upper GI GVHD was successfully controlled with or without additional steroids in all cases and had little impact on transplant outcome.

Keywords: GVHD; stem cell transplantation; endoscopy; upper gastrointestinal tract

GVHD were based on clinicopathological studies at only a few institutions in the United States.¹⁻⁸ It has been suggested that clinical features of GVHD differ by geographic area or among races because of different immunogenetic backgrounds.¹¹⁻¹⁴ Therefore, the clinical significance of upper GI GVHD in previous reports may not necessarily apply to patients outside the United States.

In most of the previous studies endoscopic and histologic examinations were limited to patients who were symptomatic after allogeneic bone marrow transplantation.¹⁻⁶ Unexplained upper GI symptoms may occur not only in allograft recipients but also in autograft recipients. Although GVHD is specific for allogeneic recipients, a GVHD-like syndrome following autologous transplantation has been reported.^{15,16} It remains unknown whether autologous GVHD can occur in the upper GI tract.

We prospectively evaluated upper GI lesions in 44 Japanese patients who underwent allogeneic or autologous hematopoietic stem cell transplantation in order to assess the incidence and clinical significance of upper GI GVHD in Japanese as well as the usefulness of prospective evaluation of upper GI tract by endoscopy.

Patients and methods

Patients

Forty-four consecutive Japanese patients who underwent allogeneic ($n = 26$) or autologous ($n = 18$) hematopoietic stem cell transplantation at the Keio University Hospital between September 1995 and February 1997 were evaluated (prospective group). We also reviewed 69 recipients of allografts ($n = 49$) or autografts ($n = 20$) between November 1988 and August 1995 (retrospective group). Three second transplants and two patients who died before engraftment were excluded from the analyses.

Table 1 shows clinical characteristics of both prospective and retrospective groups. The characteristics of both groups were comparable with respect to age, sex, diagnosis, and type of graft, but more patients in the prospective group received tacrolimus (FK 506) after transplant as GVHD prophylaxis. In both groups, recipients of allografts were conditioned with TBI more frequently than those of autografts.

Upper gastrointestinal tract acute graft-versus-host disease (upper GI GVHD) is a syndrome characterized by non-specific upper GI symptoms accompanied by histologic evidence of GVHD. Several studies on upper GI GVHD have proposed that this syndrome be considered stage I GI tract GVHD.¹⁻¹⁰ However, these investigations on upper GI

Table 1 Characteristics of prospective and retrospective groups

	Prospective group		Retrospective group	
	Allograft (n = 26)	Autograft (n = 18)	Allograft (n = 49)	Autograft (n = 20)
Median age (years) (range)	33 (14–52)	45 (19–55)	38 (16–55)	44 (12–57)
Sex (M:F)	14:12	6:12	29:20	9:11
Diagnosis				
CML	4	0	18	0
AML	9	1	13	2
MDS	2	0	9	0
ALL	8	1	7	1
NHL	2	8	1	11
HD	1	1	0	1
MM	0	4	0	3
AA	0	0	1	0
Breast Ca	0	3	0	2
Conditioning				
TBI (+)	24	0	41	6
TBI (–)	2	18	8	14
Stem cell source				
BM	26	2	47	1
PBSC	0	9	2	15
BM+PBSC	0	7	0	4
Donor				
HLA-identical sibling	19	—	37	—
HLA-matched unrelated	7	—	12	—
GVHD prophylaxis				
CYA+MTX	20	—	43	—
FK506+MTX	6	—	6	—

MDS = myelodysplastic syndrome; NHL = non-Hodgkin's lymphoma; HD = Hodgkin's disease; MM = multiple myeloma; AA = aplastic anemia; Breast Ca = breast cancer; FK506 = tacrolimus.

Endoscopic examination

Endoscopic examination was performed between day 20 and day 50 post-transplant when the effect of the conditioning regimen on the upper GI tract was minimal. Endoscopy was also performed when a patient became symptomatic or developed acute GVHD of the skin, liver, or lower GI tract. If a patient was diagnosed with upper GI GVHD, endoscopic examination was repeated until both endoscopic and histologic findings became normal.

Endoscopy was performed only if coagulation tests were normal and platelet counts were greater than $5 \times 10^4/\mu\text{l}$. The procedure was performed by a few members of staff at the Division of Gastroenterology (TY, YI, TH and TH). Biopsy specimens were taken from both normal-appearing tissue and areas with endoscopic abnormalities in the esophagus, stomach and duodenum. Informed consent was obtained from all patients. All survivors have been followed for a minimum of 6 months after transplantation.

Histologic examination

Separate biopsy specimens from each site were fixed in 10–20% buffered formalin for histology, prepared for immunohistology as recommended by the manufacturer, and placed in transport medium for viral culture. Sections of $5 \mu\text{m}$ were cut from paraffin-embedded tissue and stained with hematoxylin and eosin.

To exclude mucosal damage by viral infection simulating GVHD such as cytomegalovirus (CMV), we looked for morphologic features suggestive of viral infection, performed immunohistologic analyses using monoclonal or polyclonal antibodies, and attempted to culture the virus.^{2,3,17} CMV infection was diagnosed on the basis of morphologic features which included large cells containing amphophilic intranuclear inclusions, immunopositivity for viral markers, or a positive viral culture. Upper GI GVHD was not diagnosed if epithelial cell necrosis was observed within foci of CMV infection.

Diagnosis of GVHD

The diagnosis of upper GI GVHD was confirmed by histologic findings of GVHD and persistent upper GI symptoms as previously described.¹ Symptoms included nausea, vomiting, anorexia, epigastric pain or discomfort, and/or food intolerance. Histologic findings included single cell epithelial necrosis associated with karyorrhexic debris, dilatation of mucosal crypts or glands, and crypt abscesses or obliteration (Figure 1).

Acute GVHD in the skin and lower GI tract was diagnosed by clinical criteria and confirmed histologically in all patients, but liver acute GVHD was diagnosed clinically without histologic confirmation. Acute GVHD was graded by standard clinical criteria.¹⁸

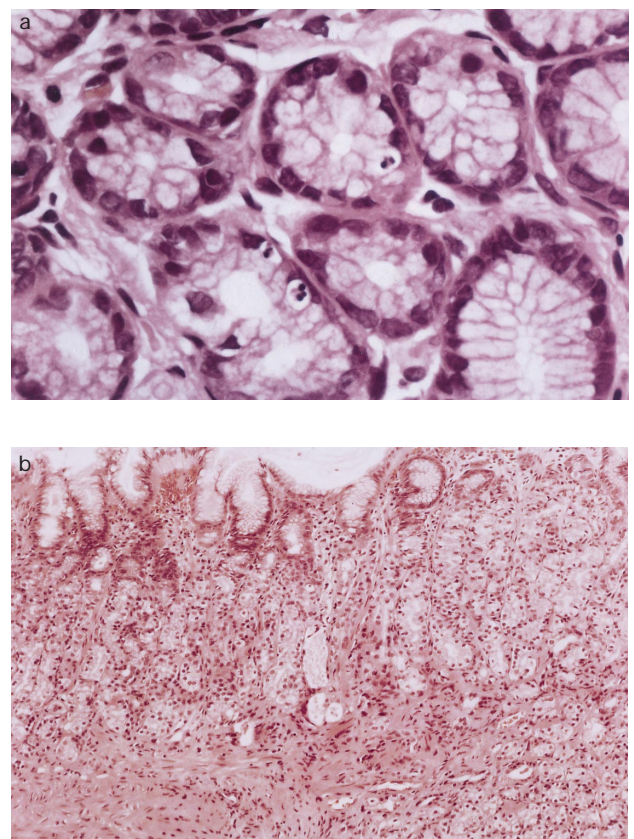


Figure 1 Histologic findings of upper GI GVHD: (a) single cell epithelial necrosis (stomach); and (b) crypt obliteration (stomach).

Statistical methods

The χ^2 analysis or Fisher's exact test using a 2 × 2 table was performed for comparison of the incidence of upper GI GVHD or its influence on transplant outcome between different patient groups.

Results

Diagnosis of upper GI GVHD

Fifty-two patients underwent transplantation between September 1995 and February 1997. Upper GI endoscopy could not be performed in eight patients because of unstable condition due to sepsis, organ failure, severe GVHD, or disease recurrence. Twenty-six allograft patients and 18 autograft patients underwent upper GI endoscopic examination.

As shown in Table 2, the incidence of upper GI GVHD was 46% in the evaluable allograft patients. No definite upper GI GVHD was diagnosed in autograft patients, and the incidence of upper GI GVHD was significantly lower in the retrospective allograft group (14%; $P < 0.005$). No patients with upper GI GVHD were diagnosed as simultaneously having CMV gastroenteritis. Three allograft recipients developed CMV gastroenteritis 2–3 weeks after complete resolution of upper GI GVHD with steroids, and were included into the group with upper GI GVHD. Non-specific gastritis or duodenitis was diagnosed in six allograft and 10 autograft recipients. Four allograft and six autograft recipients were asymptomatic. All patients with nonspecific gastritis or duodenitis were included into the group without upper GI GVHD.

Clinical characteristics of patients diagnosed with upper GI GVHD are shown in Table 3. The age of patients with upper GI GVHD was similar to that of patients without upper GI GVHD; median age was 31 years (range 15–52) vs 34 years (range 14–46). The incidence appeared lower in patients with acute lymphoblastic leukemia (ALL) or in recipients of HLA-identical sibling transplants, but these differences were not statistically significant ($P = 0.22$ and 0.19 , respectively). Sex, conditioning regimen, and GVHD prophylaxis did not affect the occurrence of upper GI GVHD.

Table 4 shows the relationship between the presence of symptoms and histologic findings of acute GVHD in the upper GI tract. Twelve of 14 symptomatic allograft patients (86%) had positive histology for GVHD and were diagnosed with upper GI GVHD. Histologic findings indicative of GVHD were not observed in any of the symptomatic autograft patients. However, histologic findings of GVHD were also recognized in five of 12 asymptomatic allograft

Table 3 Characteristics of 12 patients who developed upper GI GVHD in the prospective group

Median age (range)	31 years	(15–52)
Sex (M:F)	6:6	
Diagnosis		
CML	3	(75%) ^a
AML	6	(67%)
MDS	1	(50%)
ALL	2	(25%)
Conditioning		
TBI (+)	11	(46%) ^b
TBI (–)	1	(50%)
Graft		
HLA-identical sibling	7	(37%) ^c
HLA-matched unrelated	5	(71%)
GVHD prophylaxis		
CYA + MTX	9	(45%) ^d
FK506 + MTX	3	(50%)

% of recipients with upper GI GVHD in the group with the same diagnosis (^a), in the group receiving conditioning regimen including or not including TBI (^b), in the group with the same source of graft (^c), and in the group with the same GVHD prophylaxis (^d). MDS = myelodysplastic syndrome; FK506 = tacrolimus.

Table 4 Symptomatology and histology in the prospective groups with allograft (Allo) or autograft (Auto)

	Allo (n = 26)		Auto (n = 18)	
	Symptoms			
Histology of GVHD	(+)	(–)	(+)	(–)
(+)	12	5	0	2
(–)	2	7	4	12

patients (42%) and in two of 14 asymptomatic autograft patients (14%). The percentage of asymptomatic recipients with positive histology was somewhat higher in allogeneic transplantation, but the difference was not significant ($P = 0.19$). The degree and distribution of histologic changes of GVHD such as single cell epithelial necrosis or crypt obliteration were similar between symptomatic and asymptomatic patients. No differences in clinical or transplant characteristics between symptomatic and asymptomatic patients could be identified. Of five asymptomatic allograft patients who presented with histologic features, two had grade II acute GVHD only in the skin without chronic GVHD, two had no acute or chronic GVHD, and one had no acute GVHD but developed chronic GVHD. None developed lower GI GVHD. Two asymptomatic autograft patients, who had positive GVHD histology, did not have clinical findings suggestive of autologous GVHD, such as skin rash, diarrhea, or liver dysfunction. Two symptomatic allograft patients and four symptomatic autograft patients had no histology compatible with GVHD. They were treated with antacids and/or H-2 receptor antagonists, and their symptoms completely resolved within 1–3 weeks.

Clinical findings of upper GI GVHD

Clinical findings of upper GI GVHD were assessed on the basis of the data of seven patients in the retrospective group

Table 2 Incidence of upper GI GVHD

	Prospective group	Retrospective group
Allografts	46%* (12/26)	14% (7/49)
Autografts	0% (0/18)	0% (0/20)

* $P < 0.005$ vs the retrospective allograft group.

and 12 patients in the prospective group. Median onset of upper GI GVHD was day 34 post-transplant (range 19–73). The stomach (84%) was the most frequently involved site, followed by the duodenum (32%) and esophagus (11%). Redness was the most frequently observed endoscopic finding, followed by erosion, but ulceration was not observed in any cases. Twelve of the 19 patients with upper GI GVHD had skin acute GVHD, and two of the 12 also had lower GI GVHD simultaneously.

Response to treatment with steroids

Thirteen of the 19 patients with upper GI GVHD received prednisolone (PSL) at a dose of 1 or 2 mg/kg/day as treatment for acute GVHD. Of the 13 patients, seven received PSL as the initial treatment for upper GI GVHD while six were already receiving PSL as treatment for acute GVHD in other organs for 2–4 days before upper GI endoscopy was performed. Six patients with upper GI GVHD did not receive steroids but continued to receive the same dose of CYA or FK506 for GVHD prophylaxis. In 18 of the 19 patients, upper GI GVHD completely resolved. In one patient, upper GI GVHD recurred during tapering of PSL. No patient subsequently developed lower GI GVHD, except for the two patients in whom lower GI GVHD was already present at diagnosis of upper GI GVHD.

Influence of upper GI GVHD on transplant outcome

Of 75 patients who underwent allogeneic transplantation between November 1988 and February 1997, 73 experienced grade 0/I or II acute GVHD, and two developed grade IV acute GVHD. We divided the 73 patients into four subgroups according to the presence or absence of acute GVHD and the diagnosis of upper GI GVHD. Table 5 shows transplant outcome among these groups. Overall survival was significantly higher in patients having grade 0/I GVHD with upper GI involvement, compared with patients having grade 0/I GVHD without upper GI involvement ($P=0.011$) or grade II GVHD without upper GI involvement ($P=0.046$). Differences in early mortality rate, the incidence of chronic GVHD, or relapse rate between the four groups were not statistically significant.

Table 5 Influence of upper GI GVHD on transplant outcome

Overall GVHD grade ^a	Upper GI GVHD	Early death (%) ^c	Chronic GVHD (%)	Relapse (%)	Survival at 1 year (%)
0–I	+ ^b (n = 11)	0 (0%)	3 (27%)	0 (0%)	11 (100%)*
	– (n = 40)	6 (15%)	16 (40%)	11 (28%)	24 (60%)
II	+ (n = 8)	0 (0%)	6 (75%)	1 (13%)	6 (75%)
	– (n = 14)	2 (14%)	4 (29%)	3 (21%)	9 (64%)

^aOverall GVHD grade was assigned according to the criteria previously described.¹⁸

^b+ = presence; – = absence.

^cWithin 100 days

* $P=0.011$ vs grade 0/I without upper GI involvement, $P=0.046$ vs grade II without upper GI involvement.

Discussion

Upper GI GVHD was diagnosed in 46% of prospective allograft patients, which was significantly higher than that among the retrospective group. Investigators have reported that upper GI GVHD occurred in 10–26% of patients undergoing allogeneic bone marrow transplantation, an incidence similar to that in our retrospective group (14%).⁸ Our results suggest that upper GI GVHD has been underdiagnosed, and this syndrome may be detected more accurately if endoscopy is applied for evaluation of upper GI symptoms after allogeneic stem cell transplantation.

Wu *et al*⁵ have reported that CMV and herpes simplex virus infection of the GI tract, once the most common causes of nausea and vomiting in bone marrow transplant patients, have become rare since the introduction of antiviral prophylaxis. In our study, gancyclovir was given for positive CMV antigenemia after September 1995. Therefore, it is plausible that pre-emptive therapy with gancyclovir allows easier detection of upper GI GVHD.

In the prospective group, 86% of symptomatic allograft patients had upper GI GVHD confirmed histologically. In addition, 37% of all patients with upper GI GVHD had no other organ involvement. This suggests that upper GI GVHD should be strongly suspected regardless of the presence of other organ GVHD in allograft patients with upper GI symptoms after day 20 post-transplant. Our prospective study showed that upper GI GVHD was the major cause of persistent upper GI symptoms. Wu *et al*⁵ reported similar causes of nausea and anorexia in allogeneic marrow transplant patients. According to their report, 81% of patients symptomatic beyond day 20 post-transplant were diagnosed with acute GVHD involving the stomach.

Weisdorf *et al*¹ reported that the incidence of chronic GVHD and overall survival for patients with upper GI GVHD was similar to that for patients with grade II GVHD; they recommended that this syndrome be considered stage I gastrointestinal GVHD. In contrast, the presence of upper GI GVHD did not affect short-term survival or the incidence of chronic GVHD in our study. Moreover, upper GI GVHD was successfully reversed by steroids and did not progress to lower GI GVHD; spontaneous resolution was observed in some cases. These findings suggest that the syndrome is equivalent to grade I GVHD in the skin, and do not support the proposal that upper GI GVHD should be graded as stage I gastrointestinal GVHD. One reason for this discrepancy may be differences in immunogenetic background. To clarify this point, analyses of clinical features should be carried out and the significance of upper GI GVHD ascertained in various patient populations or geographic areas.

Forbes *et al*⁹ have reported on prospective endoscopic appearance of the upper GI tract in both allogeneic and autologous bone marrow transplant patients, regardless of symptoms. In their report, only three of 41 allograft patients were diagnosed with upper GI GVHD. Although it is difficult to compare their study with ours since the details of symptoms and the diagnostic criteria for upper GI GVHD were not described in their study, the incidence of upper GI GVHD seems to be higher in Japanese than in West-erners. It is noteworthy that our study suggests a high inci-

dence of upper GI GVHD in contrast to a previous report showing a low incidence of acute GVHD of other organs in Japanese.¹³

Unexplained upper GI symptoms occur not only in allograft recipients but also in autograft recipients. Although GVHD is considered to be specific for the allogeneic setting, so-called autologous GVHD has been reported.^{15,16} This study is the first to show that definitive upper GI GVHD is specific to allogeneic transplantation. In all symptomatic patients without histologic findings of GVHD, their symptoms resolved with antacids and/or H-2 receptor antagonists within 1–3 weeks, and none developed definite upper or lower GI tract GVHD. Therefore, although the possibility of sampling errors cannot be ruled out, we believe that these upper GI symptoms did not represent upper GI GVHD.

Notably, histologic findings of GVHD were found in some asymptomatic patients. Histologic changes in the asymptomatic patients could not be distinguished from those in the symptomatic patients. The clinical significance of these findings remains unclear. It is possible that the histologic findings of GVHD observed in asymptomatic patients reflect subclinical GVHD in the upper GI tract.^{19,20} Alternatively, they may reflect histologic damage caused by etiologies other than a GVH reaction. Several investigators have reported GVHD-like histopathologic findings in immunodeficiency states including HIV infection, common variable immunodeficiency, and severe T cell deficiency, and also following renal transplantation.^{7,21–23} Hematopoietic stem cell transplantation can lead to immunodeficiency states due to myeloablative conditioning regimens or use of immunosuppressants. It is possible that GVHD-like histologic changes are related to immunodeficiency in some of our asymptomatic patients.

Washington *et al*⁷ reported a histologic study of gastric GVHD. In their study, the reproducibility of diagnosis and recognition of histologic features of gastric GVHD were based on blinded reviews of 56 gastric biopsy specimens (24 from patients after allogeneic BMT or unrelated umbilical cord blood transplantation and 32 from control patients who did not undergo BMT). The blinded histologic diagnosis of gastric GVHD had a false-positivity rate of 24%. False-positive results occurred in CMV gastritis, HIV infection, primary immunodeficiency, and after renal transplantation. These authors suggested that histologic distinctions between GVHD and CMV infection were difficult to make and that GVHD could be confused with histologic changes seen in HIV infection and other immunodeficiency states. Their study and ours suggest that confirmation of the diagnosis of upper GI GVHD requires not only symptomatology and histology but also sufficient exclusion of other etiologies.

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References

- 1 Weisdorf DJ, Snover DC, Haake R *et al*. Acute upper gastrointestinal graft-versus-host disease: clinical significance and response to immunosuppressive therapy. *Blood* 1990; **76**: 624–629.
- 2 Roy J, Snover DC, Weisdorf SA *et al*. Simultaneous upper and lower endoscopic biopsy in the diagnosis of intestinal graft-versus-host disease. *Transplantation* 1991; **51**: 642–646.
- 3 Snover DC, Weisdorf SA, Vercellotti GM *et al*. A histopathologic study of gastric and small intestinal graft-versus-host disease following allogeneic bone marrow transplantation. *Hum Pathol* 1985; **16**: 387–392.
- 4 Spencer GD, Hackmann RC, McDonald GB *et al*. A prospective study of unexplained nausea and vomiting after marrow transplantation. *Transplantation* 1986; **42**: 602–607.
- 5 Wu D, Ponc R, Brentnall T *et al*. Causes of nausea and anorexia in marrow transplant patients: a prospective study. *Gastroenterology* 1995; **108** (Suppl.): A945.
- 6 Terdiman JP, Linker CA, Ries CA *et al*. The role of endoscopic evaluation in patients with suspected graft-versus-host disease after allogeneic bone-marrow transplantation. *Endoscopy* 1996; **28**: 680–685.
- 7 Washington K, Bentley RC, Green A *et al*. Gastric graft-versus-host disease: a blind histologic study. *Am J Surg Pathol* 1997; **21**: 1037–1046.
- 8 Przepiorka D, Weisdorf DJ, Martin P *et al*. Consensus conference on acute GVHD grading. *Bone Marrow Transplant* 1995; **15**: 825–828.
- 9 Forbes GM, Rule SAJ, Herrmann RP *et al*. A prospective study of screening upper gastrointestinal (GI) endoscopy prior to and after bone marrow transplantation (BMT). *Aust NZ J Med* 1995; **25**: 32–36.
- 10 Appleton AL, Sviland L, Pearson DJ *et al*. The need for endoscopic biopsy in the diagnosis of upper gastrointestinal graft-versus-host disease. *J Pediatr Gastroenterol Nutr* 1993; **16**: 183–185.
- 11 Goulmy E, Schipper R, Pool J *et al*. Mismatch of minor histocompatibility antigens between HLA identical donors and recipients and the development of graft-versus-host disease after bone marrow transplantation. *New Engl J Med* 1996; **334**: 281–285.
- 12 Smyth LA, Herrmann RP, Christiansen FT *et al*. Major histocompatibility complex influences the development of acute graft-versus-host disease in MHC-matched adult allogeneic bone marrow transplantation. *Transplant Proc* 1993; **25**: 1276–1278.
- 13 Morishima Y, Morishita Y, Tanimoto M *et al*. Low incidence of acute graft-versus-host disease by the administration of methotrexate and cyclosporine in Japanese leukemia patients after bone marrow transplantation from human leukocyte antigen compatible siblings: possible role of genetic homogeneity. *Blood* 1989; **74**: 2252–2256.
- 14 Imanishi T, Akaza A, Kimura A *et al*. Allele and haplotype frequencies for HLA and complement loci in various ethnic groups. In: Tsuji K, Aizawa M, Sasazuki T (eds). *Proceedings of the Eleventh International Histocompatibility Workshop and Conference*. Oxford University Press: New York, 1991, pp 1065–1220.
- 15 Thein SL, Goldman JM, Galton DAG. Acute 'graft-versus-host disease' after autografting for chronic granulocytic leukemia in transformation. *Ann Intern Med* 1981; **94**: 210–211.
- 16 Hood AF, Vogelsang GB, Black LP *et al*. Acute graft-versus-host disease, development following autologous and syngeneic bone marrow transplantation. *Arch Dermatol* 1987; **123**: 745–750.
- 17 Snover DC. Mucosal damage simulating acute graft-versus-

- host reaction in cytomegalovirus colitis. *Transplantation* 1985; **39**: 669–670.
- 18 Glucksberg H, Storb R, Fefer A *et al*. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. *Transplantation* 1974; **19**: 295–304.
- 19 Sullivan KM, Witherspoon RP, Storb R *et al*. Prednisone and azathioprine compared with prednisone and placebo for treatment of chronic graft-versus-host disease: prognostic influence of prolonged thrombocytopenia after allogeneic marrow transplantation. *Blood* 1988; **72**: 546–554.
- 20 Loughran TP, Sullivan K, Morton T *et al*. Value of day 100 screening studies for predicting the development of chronic graft-versus-host disease after allogeneic bone marrow transplantation. *Blood* 1990; **76**: 228–234.
- 21 Kotler DP, Gaetz HP, Lange M *et al*. Enteropathy associated with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; **101**: 421–428.
- 22 Lee EL, Clouse RE, Aliperti G, DeSchryver-Keckemati K. Small intestinal lesion resembling graft-versus-host disease. *Arch Pathol Lab Med* 1991; **115**: 529–532.
- 23 Snover DC, Filipovich AH, Ramsay NKC *et al*. Graft-versus-host disease-like histopathologic findings in pre-bone marrow transplantation biopsies of patients with severe T cell deficiency. *Transplantation* 1985; **39**: 95–97.