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Drugs as a Frequent Cause of Acute Rash in Patients after CD34$^+$-Selected Peripheral Blood Stem Cell Transplantation

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A B S T R A C T

Although histopathological differences have been reported between acute graft-versus-host disease (aGVHD) rash and non-aGVHD rash in CD34$^+$-selected peripheral blood stem cell transplantation (PBSCT) recipients, skin biopsy alone is usually insufficient to determine rash etiology. As such, distinguishing inflammatory non-aGVHD rashes, such as drug eruptions, from cutaneous aGVHD after CD34$^+$-selected PBSCT remains challenging and relies on clinical presentation. This study aimed to identify etiologies of skin rash in the first year after CD34$^+$-selected PBSCT and to assess whether laboratory serologic markers, transplant characteristics, and rash morphology and symptomatology aid in differentiation of cutaneous aGVHD rash versus non-aGVHD rash. We conducted a retrospective study of 243 adult patients who underwent CD34$^+$-selected PBSCT at Memorial Sloan Kettering Cancer Center between 2008 and 2011. Among this cohort of transplant recipients, only 43 patients (17.7%) developed cutaneous aGVHD. A total of 152 patients (63%) were identified with rash within 1 year after PBSCT. The proportion of patients who experienced peripheral eosinophilia was not different between those with an aGVHD versus non-aGVHD rash ($P \geq .90$), nor when stratified by CD34$^+$ selection method (Isolex, $P = .70$; CliniMACS, $P \geq .90$). The proportion of patients with pruritus was also not different between those with an aGVHD rash versus non-aGVHD rash ($P = .20$), or when stratified by CD34$^+$ selection modality (Isolex, $P = .20$; CliniMACS, $P = .50$). The most common cause of non-aGVHD rash among those with a clear etiology was drug (39% of Isolex; 26% of CliniMACS). Single drug culprits were identified in 51% of drug rashes. The most commonly reported offending agents included antibiotics, keratinocyte growth factor, chemotherapy, and recombinant glycosylated human IL-7.
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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for hematologic malignancies. Acute graft-versus-host disease (aGVHD) may follow allo-HSCT as a multisystem complication of the treatment. Compared with T cell-replete allo-HSCT, CD34$^+$-selected allo-HSCT is associated with a reduced incidence of cutaneous aGVHD (14%), decreased severity of aGVHD, and similar curative efficacy in appropriately selected patients [1]. However, allo-HSCT recipients are exposed to complex drug regimens in the setting of extended immunocompromised states, raising the risk for drug eruptions and viral exanthems that may cause rash [2].

In allo-HSCT recipients, skin is often the first organ demonstrating involvement by aGVHD [3,4]. At the onset of aGVHD, >80% of patients have skin involvement [3]. Similar to a morbilliform drug eruption, aGVHD presents with a possibly pruritic, erythematous morbilliform rash [3]. aGVHD rash may be the presenting manifestation of systemic aGVHD at a time when other clinical signs and symptoms of aGVHD are absent, leading to delays in timely and accurate diagnosis.

Accurate diagnosis of cutaneous aGVHD remains challenging and relies on correlation of clinical history, physical examination, and laboratory data. Although cutaneous aGVHD has distinguishing characteristics (eg, ear involvement, follicular involvement) from rashes unrelated to aGVHD, the findings are frequently ambiguous and overlap with other inflammatory post-transplantation cutaneous conditions (Figure 1) [5,6]. The utility of a skin biopsy in delineating between aGVHD and a drug rash is limited [7-10]. In addition, the concomitant presence of a morbilliform rash with peripheral

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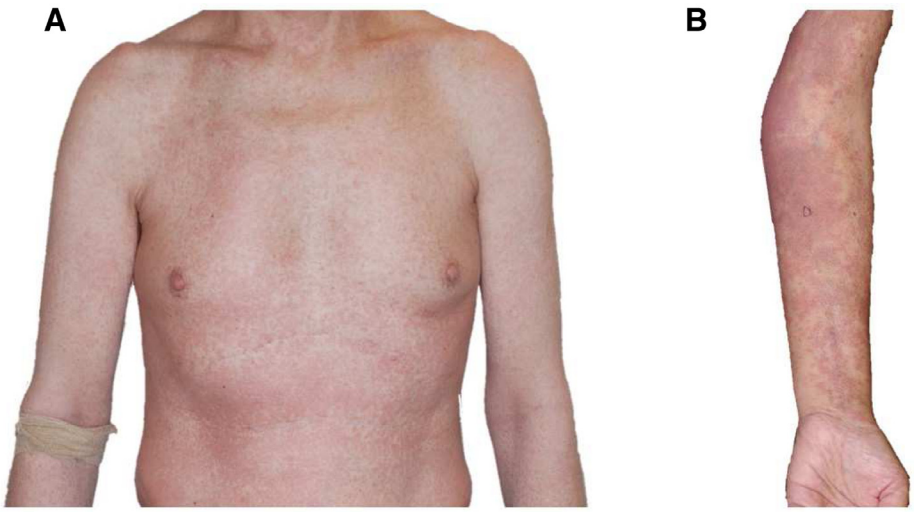

Figure 1. Clinical photography of morbilliform eruptions due to cutaneous aGVHD morbilliform eruption (A) and drug rash (from voriconazole versus spironolactone) (B).

eosinophilia may mislead clinicians to favor a diagnosis of drug eruption after allo-HSCT, because an elevated eosinophil count is part of the diagnostic criteria for drug reaction with eosinophilia and systemic symptoms (DRESS; also known as drug-induced hypersensitivity syndrome) [11]. However, elevated peripheral and tissue eosinophil levels are also associated with the occurrence of aGVHD [5,6,12-14]. Incorrect attribution of rash to drugs instead of to aGVHD, with a subsequent delay in aGVHD management, may lead to increased morbidity and mortality and decreased quality of life [15].

In this retrospective study, we sought to assess the features and common etiologies of a cohort of 152 patients with cutaneous aGVHD rash or non-aGVHD rash within 1 year after undergoing CD34$^+$-selected allo-HSCT. These findings may guide clinicians in earlier diagnosis and management of cutaneous aGVHD rash and non-aGVHD rash.

METHODS

Patient and Graft Characteristics

This analysis used a clinical research database of all adult patients who underwent CD34$^+$-selected allogeneic peripheral blood stem cell transplantation (PBSCT) at Memorial Sloan Kettering Cancer Center (MSKCC) between January 1, 2008, and May 31, 2011. The MSKCC Adult Bone Marrow Transplantation database, verified by primary source documents, provided data on patient characteristics and transplantation-related outcomes. Each patient was assigned a disease risk using the Disease Risk Index for allo-HSCT [16]. Patient HLA typing used a 5-allele level high-resolution, DNA sequence-specific oligonucleotide typing for HLA-A, -B, -C, -DRB1, and -DQ. Although donor selection used matching at 10 HLA alleles, only 8 HLA allele matching at -A, -B, -C, and -DRB1 were used in this analysis. The study cohort included related and unrelated donors.

Donor peripheral blood stem cells were mobilized by granulocyte-colony stimulating factor. Before transplantation, CD34$^+$ hematopoietic progenitor cells were selected using the Isolex 300i Magnetic Cell Separator (Baxter, Deerfield, IL), followed by additional T cell rosetting with neuraminidase-treated sheep erythrocytes, or using the CliniMACS CD34$^+$ Reagent System (Miltenyi Biotech, Gladbach, Germany) [17,18]. The Isolex system was in use between 2008 and 2010 and then became commercially unavailable. Grafts were infused within 48 hours of CD34$^+$ selection.

Conditioning Regimens

Pretransplantation conditioning regimens are described in Table 1. Granulocyte-colony stimulating factor (5 μg/kg/day) was given to all patients starting on day 7 and continuing until an absolute neutrophil count recovery of $>2.0 \times 10^9$/L was achieved.

GVHD Prophylaxis and Diagnosis

To prevent allograft rejection, most patients received rabbit or horse antithymocyte globulin before transplantation. Prophylactic immunosuppressants were not used after CD34$^+$-selected allo-HSCT.

Acute GVHD was clinically diagnosed by the presence of acute erythematous and/or morbilliform rash, and was histologically confirmed when clinically indicated to confirm the diagnosis if other clinical parameters suggested GVHD and to exclude other processes with specific histological features (eg, vasculitis, fungal or bacterial sepsis, leukemia cutis) and graded according to the International Bone Marrow Transplant Registry classification, with grades A to D labeled grades I to IV [19]. Cutaneous aGVHD was quantified by percent body surface area of active erythematous rash; rashes that were pink, fading, or turning to brown were not included in the assessment, because these findings indicate resolving lesions. Cutaneous aGVHD was staged according to percent body surface area covered by the rash (stage 1: $<$25% of body surface area; stage 2: 25% to 50%; stage 3: $>$50%; stage 4: erythroderma with bullae) [20]. The onset date of cutaneous aGVHD was determined by the date of initiation of topical therapy and date of skin biopsy or, if this is unavailable, date of initial clinical diagnostic description. Subsequently, a panel of transplantation clinicians reviewed the grading and reached a consensus on maximum aGVHD stage and grade. This consensus diagnosis was used for data analysis.

Patient Selection

First, non-aGVHD rash was identified by chart review from the date of PBSCT through 1 year after PBSCT using dermatology visit notes or by extraction of International Classification of Diseases, Ninth Revision (ICD-9) codes 528, 690 to 701, 709, 782, E930, and E947 for skin lesion or rash. Patients without documented rash, or with rash defined by skin infection or chronic cutaneous GVHD rash, were excluded.

For patients identified with cutaneous aGVHD or non-aGVHD skin rash, peripheral absolute eosinophils and percent eosinophils were recorded from clinical laboratory reports on the initial day of rash presentation. Thirteen patients were missing peripheral eosinophil laboratory data. Eosinophilia was defined as above the laboratory limit (absolute eosinophils, $>$.8 K/μL; percent eosinophils, $>$7.0%); however, absolute eosinophils were excluded from the final analysis due to limited events of absolute eosinophilia.

Rash in patients with aGVHD and those without aGVHD were identified as pruritic or nonpruritic by chart review on the day of initial rash presentation. Single drug culprits were identified in 51% of non-aGVHD drug rashes by chart documentation of the offending agent.

Skin biopsies were performed and available in 35% of patients, including 22 of 43 patients in the cutaneous aGVHD group and 31 of 109 in the non-aGVHD group. The histopathological differences between cutaneous aGVHD and non-aGVHD rash have been reported previously [5]. At our institution, skin biopsy is not routinely performed for morbilliform eruptions after allo-HSCT, given its limited diagnostic utility for differentiating cutaneous aGVHD from drug or viral eruptions [7,8,10,21].

Statistical Analysis

Fisher's exact test and the Kruskal-Wallis test were used for categorical and continuous variables, respectively, to test the association between selected variables and cutaneous aGVHD rash versus non-aGVHD rash. Given the decreased incidence of aGVHD with Isolex versus CliniMACS CD34$^+$-selected methods, we established Isolex and CliniMACS CD34$^+$-selected groups and assessed cutaneous aGVHD and non-aGVHD rash within these 2 CD34$^+$ selection modalities when sample size allowed [1].

Table 1
Patient Characteristics

Characteristic	Total (N = 152)	aGVHD (N = 43; 28.2%)	Non-aGVHD (N = 109; 71.7%)	*P* Value
Days to rash, median (IQR)	60 (26-155)	71 (32-158)	53 (25-146)	.40
Age, yr, median (IQR)	56 (46-63)	56 (49-64)	55 (44-63)	.40
CD 34$^+$ selection method, n (%)				<**.001**
Isolex	78 (51.3)	11 (25.6)	67 (61.5)	
CliniMACS	74 (48.7)	32 (74.4)	42 (38.5)	
Absolute eosinophils, n (%)				NA
≤.8 K/μL	149 (99)	43 (100)	106 (97.2)	
>.8 K/μL	2 (1.3)	0 (0)	2 (1.8)	
NA	1	0	1	
% eosinophils, n (%)				>.90
≤7	124 (88.6)	38 (88.4)	86 (88.7)	
>7	16 (11.4)	5 (11.6)	11 (11.3)	
NA	12	0	12	
Pruritus, n (%)				.20
No	61 (40.1)	21 (48.8)	40 (36.7)	
Yes	91 (59.9)	22 (51.2)	69 (63.3)	
Recipient sex, n (%)				.70
Female	58 (38.2)	15 (34.9)	43 (39.4)	
Male	94 (61.8)	28 (65.1)	66 (60.6)	
Donor sex, n (%)				.50
Female	58 (38.2)	14 (32.6)	44 (40.4)	
Male	94 (61.8)	29 (67.4)	65 (59.6)	
Recipient CMV serostatus, n (%)				.40
Inconclusive (NA for *P* value calculation)	3 (2)	1 (2.3)	2 (1.8)	
Negative	72 (47.4)	24 (55.8)	48 (44.0)	
Positive	77 (50.7)	18 (41.9)	59 (54.1)	
Diagnosis, n (%)				.80
Acute leukemia*	85 (55.9)	22 (51.2)	63 (57.8)	
CML/CMML/MDS/MPN	36 (23.7)	11 (25.6)	25 (22.9)	
MM	18 (11.8)	5 (11.6)	13 (11.9)	
Other†	13 (8.6)	5 (11.6)	8 (7.3)	
Risk, n (%)				.30
High	46 (30.3)	10 (23.3)	36 (33.0)	
Intermediate	18 (11.8)	8 (18.6)	10 (9.2)	
Low	84 (55.3)	24 (55.8)	60 (55.0)	
NA	4 (2.6)	1 (2.3)	3 (2.8)	
Conditioning regimen, n (%)				.50
Bu/Flu/Mel	103 (67.8)	28 (65.1)	75 (68.8)	
TBI-based‡	43 (28.3)	12 (27.9)	31 (28.4)	
Other§	6 (3.9)	3 (7.0)	3 (2.8)	
HLA match, n (%)				.60
Related	66 (43.4)	16 (37.2)	50 (45.9)	
Unrelated identical	47 (30.9)	14 (32.6)	33 (30.3)	
Unrelated nonidentical	39 (25.7)	13 (30.2)	26 (23.9)	

P values were calculated using Fisher's exact test for categorical variables (NA values removed before calculation) and the Kruskal-Wallis test for continuous variables. NA indicates not available; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative disorder; MM, multiple myeloma; Bu, busulfan; Mel, melphalan; Flu, fludarabine; TBI, total body irradiation.

* Acute leukemias include acute myelogenous leukemia, acute lymphoblastic leukemia, acute biphenotypic leukemia, and acute promyelocytic leukemia.

† Other: Non-Hodgkin's lymphoma, hemophagocytic lymphohistiocytosis, T cell prolymphocytic leukemia, familial hemophagocytic lymphohistiocytosis or severe aplastic anemia.

‡ TBI-based: TBI/thiotepa/cyclophosphamide or TBI/thiotepa/fludarabine.

§ Other: Carmustine/cytarabine/etoposide/alemtuzumab, clofarabine/hydrocortisone/thiotepa /melphalan or thiotepa/fludarabine /cyclophosphamide.

RESULTS

Patient Demographics and Clinical Characteristics

Among the 243 CD34$^+$-selected PBSCT recipients, 132 underwent CliniMACS CD34$^+$ selection and 111 received Isolex CD34$^+$ selection. Among these 243 patients, 155 were assigned a dermatologic ICD-9 code within 1 year after undergoing allo-HSCT. One patient was excluded due to lack of chart documentation confirming rash at the time of ICD-9 code assignment, 1 patient was excluded for a rash associated with chronic cutaneous GVHD, and 1 patient was excluded for a diagnosis of herpetic skin rash (infection). Thus, a total of 152 patients (63%) were included in our

analysis. Of these patients, 78 had received grafts CD34$^+$-selected with the Isolex system and 74 had received grafts CD34$^+$-selected with the CliniMACS system. Ninety-one patients (60%) with rash had pruritus, including 69 (63%) with cutaneous aGVHD rash and 22 (51%) with drug rash. Sixteen patients (11%; 16 of 140 reported values) with rash had an elevated percentage of eosinophils (defined as >7%), and 2 patients (1%; 2 of 151 reported values) had absolute eosinophilia. Patient and graft characteristics are summarized in Tables 1 to 3. ICD-9 codes identified in the chart review are listed Table 4.

Among patients who developed a rash, days to appearance of rash (P= .40), patient age (P= .40), patient sex (P= .70), donor sex (P= .50), patient cytomegalovirus (CMV) status (P= .40), disease risk (P= .30), conditioning regimen (P= .50), or HLA match (P= .60) did not differ between patients with cutaneous aGVHD rash and those with non-aGVHD rash based on Fisher's exact test and the Kruskal-Wallis test (Table 1). Peripheral percent eosinophils was not associated with either a cutaneous aGVHD rash or non-aGVHD rash after allo-HSCT ($P\geq$ .90) (Tables 1 to 3). Patients with cutaneous aGVHD rash experienced less pruritus than those with

Table 2
Characteristics of Patients Treated with Isolex

Characteristic	Total (N = 78)	aGVHD (N = 11; 14.1%)	Non-aGVHD (N = 67; 85.9%)	*P* Value
Days to rash, median (IQR)	71 (24-146)	71 (56-150)	60 (22-146)	.30
Age, yr, median (IQR)	54 (43-63)	53 (48-60)	54 (42-63)	.90
Absolute eosinophils, n (%)				NA
≤.8 K/μL	77 (98.7)	11 (100)	66 (98.5)	
>.8 K/μL	1 (1.3)	0 (0)	1 (1.5)	
% eosinophils, n (%)				.70
≤7	58 (85.2)	9 (81.8)	49 (86)	
>7	10 (14.7)	2 (18.2)	8 (14)	
NA	10	0	10	
Pruritus, n (%)				.20
No	33 (42.3)	7 (63.6)	26 (38.8)	
Yes	45 (57.7)	4 (36.4)	41 (61.2)	
Recipient sex, n (%)				>.90
Female	28 (35.9)	4 (36.4)	24 (35.8)	
Male	50 (64.1)	7 (63.6)	43 (64.2)	
Donor sex, n (%)				.11
Female	32 (41)	2 (18.2)	30 (44.8)	
Male	46 (59)	9 (81.8)	37 (55.2)	
Recipient CMV serostatus, n (%)				>.90
Inconclusive (NA for *P* value calculation)	2 (2.6)	0 (0)	2 (3.0)	
Negative	35 (44.9)	5 (45.5)	30 (44.8)	
Positive	41 (52.6)	6 (54.5)	35 (52.2)	
Diagnosis				.01
Acute leukemia*	54 (69.2)	4 (36.4)	50 (74.6)	
CML/MDS/MPN	8 (10.3)	4 (36.4)	4 (6.0)	
MM	8 (10.3)	1 (9.1)	7 (10.4)	
Other†	8 (10.3)	2 (18.2)	6 (9.0)	
Risk, n (%)				.50
High	27 (34.6)	3 (27.3)	24 (35.8)	
Intermediate	11 (14.1)	3 (27.3)	8 (11.9)	
Low	40 (51.3)	5 (45.5)	35 (52.2)	
Conditioning regimen, n (%)				.60
Bu/Flu/Mel	51 (65.4)	6 (54.5)	45 (67.2)	
TBI-based‡	25 (32.1)	5 (45.5)	20 (29.9)	
Other§	2 (2.6)	0 (0)	2 (3.0)	
HLA match, n (%)				.80
Related	34 (43.6)	5 (45.5)	29 (43.3)	
Unrelated identical	23 (29.5)	4 (36.4)	19 (28.4)	
Unrelated nonidentical	21 (26.9)	2 (18.2)	19 (28.4)	

P values were calculated using Fisher's exact test for categorical variables (NA values removed before calculation), and the Kruskal-Wallis test for continuous variables.

* Acute leukemias include acute myelogenous leukemia, acute lymphoblastic leukemia, acute biphenotypic leukemia, and acute promyelocytic leukemia.

† Other: Non-Hodgkin's lymphoma, hemophagocytic lymphohistiocytosis, T cell prolymphocytic leukemia, familial hemophagocytic lymphohistiocytosis or severe aplastic anemia.

‡ TBI-based: TBI/thiotepa/cyclophosphamide or TBI/thiotepa/fludarabine.

§ Other: Carmustine/cytarabine/etoposide/alemtuzumab, clofarabine/hydrocortisone/thiotepa /melphalan or thiotepa/fludarabine /cyclophosphamide.

Table 3
Characteristics of Patients Treated with CliniMACS

Characteristic	Total (N = 74)	aGVHD (N = 32; 43%)	Non-aGVHD (N = 42; 57%)	*P* Value
Days to rash, median (IQR)	54 (32-158)	75 (30-156)	53 (34-154)	>.90
Age, yr, median (IQR)	58 (47-63)	58 (50-63)	58 (47-63)	.90
Absolute eosinophils, n (%)				NA
≤.8 K/μL	72 (98.6)	32 (100)	40 (97.6)	
>.8 K/μL	1 (1.4)	0 (0)	1 (2.4)	
NA	1	0	1	
% eosinophils, n (%)				>.90
≤7	66 (91.7)	29 (90.6)	37 (92.5)	
>7	6 (8.3)	3 (9.4)	3 (7.5)	
NA	2	0 (0)	2	
Pruritus, n (%)				.50
No	28 (37.8)	14 (43.8)	14 (33.3)	
Yes	46 (62.2)	18 (56.2)	28 (66.7)	
Recipient sex, n (%)				.50
Female	30 (40.5)	11 (34.4)	19 (45.2)	
Male	44 (59.5)	21 (65.6)	23 (54.8)	
Donor sex, n (%)				.80
Female	26 (35.1)	12 (37.5)	14 (33.3)	
Male	48 (64.9)	20 (62.5)	28 (66.7)	
Recipient CMV serostatus, n (%)				.12
Inconclusive (NA for *P* value calculation)	1 (1.4)	1 (3.1)	0 (0)	
Negative	37 (50.0)	19 (59.4)	18 (42.9)	
Positive	36 (48.6)	12 (37.5)	24 (57.1)	
Diagnosis				.058
Acute leukemia*	31 (41.9)	18 (56.3)	13 (31.0)	
CML/MDS/MPN	28 (37.8)	7 (21.9)	21 (50.0)	
MM	10 (13.5)	4 (12.5)	6 (14.3)	
Other†	5 (6.8)	3 (9.4)	2 (4.8)	
Risk, n (%)				.40
High	19 (25.7)	7 (21.9)	12 (28.6)	
Intermediate	7 (9.5)	5 (15.6)	2 (4.8)	
Low	44 (59.5)	19 (59.4)	26 (59.5)	
NA	4 (5.4)	1 (3.1)	3 (7.1)	
Conditioning regimen, n (%)				.50
Bu/Flu/Mel	52 (70.3)	22 (68.8)	30 (71.4)	
TBI-based‡	18 (24.3)	7 (21.9)	11 (26.2)	
Other§	4 (5.4)	3 (9.4)	1 (2.4)	
HLA match, n (%)				.20
Related	32 (43.2)	11 (34.4)	21 (50)	
Unrelated identical	24 (32.4)	10 (31.2)	14 (33.3)	
Unrelated nonidentical	18 (24.3)	11 (34.4)	7 (16.7)	

P values were calculated using Fisher's exact test for categorical variables (NA values removed before calculation), and the Kruskal-Wallis test for continuous variables.

* Acute leukemias include acute myelogenous leukemia, acute lymphoblastic leukemia, acute biphenotypic leukemia, and acute promyelocytic leukemia.

† Other: Non-Hodgkin's lymphoma, hemophagocytic lymphohistiocytosis, T cell prolymphocytic leukemia, familial hemophagocytic lymphohistiocytosis or severe aplastic anemia.

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§ Other: Carmustine/cytarabine/etoposide/alemtuzumab, clofarabine/hydrocortisone/thiotepa /melphalan or thiotepa/fludarabine /cyclophosphamide.

non-aGVHD rash; however, the difference did not reach statistical significance (P= .20) (Tables 1 to 3).

CD34⁺-Selection Method

Rash due to aGVHD was seen in 32 of the 132 patients who underwent CliniMACS CD34⁺ selection (24.2%), compared with only 11 of 111 in the Isolex group (9.9%). Among the patients who developed rash, a statistically significantly smaller proportion of patients had a rash from cutaneous aGVHD after CD34⁺ selection by Isolex compared with CliniMACS (26% versus 74%; P< .001) (Table 1). Among non-aGVHD rashes, the proportion of patients with a rash due to drugs was significantly higher in the Isolex group compared with the CliniMACS group (39% versus 26%) (Table 5).

Isolex

Of the 78 patients in the Isolex group who developed a rash, 11 (14%) were diagnosed with cutaneous aGVHD rash and 67 (86%) were diagnosed with non-aGVHD rash. Among these patients, the median time to onset was 71 days for

Table 4
ICD-9 Codes

ICD-9 Code	Description
528	Drug dermatitis
690	Seborrheic dermatitis, nonspecific
692	Dermatitis
693	Drug dermatitis
695	Erythema
696	Pityriasis rosea
698	Pruritic disorder
701	Keratoderma, acquired
709	Skin disorder
782	Nonspecific skin eruption
E930	Adverse effect of penicillin
E947	Adverse effect of medicine

Table 5
Non-aGVHD Rash, Patient and Graft Characteristics after CD34$^+$-Selected Allo-HSCT

Etiology	Isolex, n (%)	CliniMACS, n (%)
Drug eruption/hypersensitivity	26 (39)	11 (26)
Inflammatory folliculitis	0	3 (7)
Dermatitis, seborrheic	1 (1)	2 (5)
Dermatitis, contact	2 (3)	0
Multifactorial or unclear	38 (57)	26 (62)

cutaneous aGVHD rash and 60 days for non-aGVHD rash. Data on peripheral percent eosinophils and absolute eosinophil count were available in 57 and 67 patients, respectively, with a non-aGVHD rash and in 11 patients (for both) with a cutaneous aGVHD rash (Table 2). There were no significant differences in the proportion of patients with eosinophilia (defined as percent eosinophils >7%; P= .70) or pruritus (P= .20) between patients with a cutaneous aGVHD rash and those with a non-aGVHD rash.

CliniMACS

CD34$^+$-selection by CliniMACS was used in 74 patients who developed a rash. Among these patients, 32 (43%) developed cutaneous aGVHD. The median onset of rash was 75 days for those with a cutaneous aGVHD rash and 53 days for those with a non-aGVHD rash. Peripheral percent eosinophils and absolute eosinophil counts were available in 40 and 41 patients, respectively, with a non-aGVHD rash and in 32 patients (for both) with a cutaneous aGVHD rash. In the CliniMACS group, there were no differences in the proportion of patients with eosinophilia (P>.90) and pruritus (P= .50) between patients with cutaneous aGVHD rash and those with a non-aGVHD rash (Table 3).

Table 7
Drug Culprits in Non-aGVHD Skin Rash (N = 37)

Drug Class	Number (%)
Antibiotic	9 (24)
Antihypertensive	1 (3)
Antithymocyte globulin	1 (3)
Chemotherapy	2 (5)
Diuretic	1 (3)
Recombinant glycosylated human IL-7	2 (5)
Keratinocyte growth factor	3 (8)
Unclear/multiple possible etiologies	18 (49)

Histopathology

Fifty-three of 152 patients underwent skin biopsy of acute exanthem (Table 6). Histopathological analysis revealed evidence of aGVHD in 25 patients, but a clinical diagnosis of cutaneous aGVHD was made in only 15 of these patients (60%). Histology showed evidence of drug eruption in 37 patients; however, the final clinical diagnosis attributed 10 of these rashes to aGVHD (27%). In 4 patients, biopsy specimens showed no histological signs of GVHD or drug rash, yet a clinical diagnosis of cutaneous GVHD was reported in 2 of these patients (50%).

aGVHD Severity

Stage and grade of cutaneous aGVHD are described in Table 8. Of those patients who developed cutaneous aGVHD, most (51%) developed skin stage 3 in both the Isolex group (73%) and the CliniMACs group (44%). Overall aGVHD grade was grade III or higher in 73% of the Isolex patients and 50% of the CliniMACS patients with cutaneous aGVHD rash.

Non-aGVHD Rash Etiology

Inflammatory causes of non-aGVHD skin rash are listed in Table 5. Among the patients with a clear etiology, the most common cause of non-aGVHD rash was a drug (39% in the Isolex group and 26% in the CliniMACS group). Other etiologies of non-aGVHD skin rash seen at much lower frequencies included contact dermatitis, inflammatory folliculitis, and seborrheic dermatitis. Single drug culprits were identified in 51% of drug rashes (Table 7) The most common offending drugs included antibiotics, chemotherapy, keratinocyte growth factor, and recombinant glycosylated human IL-7. Other drugs causing skin eruptions included antihypertensives, antithymocyte globulin, and diuretics.

DISCUSSION

CD34$^+$-selected grafts used in PBSCT have a favorable safety and efficacy profile in reducing the overall incidence of aGVHD [1,18,22]. However, most previous studies on clinical or laboratory markers predictive of aGVHD were performed in

Table 6
Skin Biopsy Histopathological Diagnosis versus Final Clinical Rash Diagnosis

Histopathological Diagnosis from Skin Biopsy Report	Final Diagnosis of GVHD Rash, n	Final Diagnosis of non-GVHD Rash, n
Consistent with GVHD, not suggestive of drug eruption	10	2
Consistent with GVHD, somewhat suggestive of drug eruption	2	2
Signs of both GVHD and drug eruption	1	3
Consistent with drug eruption, some signs of GVHD	2	3
Consistent with drug eruption, no signs of GVHD	5	19
No diagnostic features of drug or GVHD	2	2

Table 8
Severity of aGVHD Rash

aGVHD Severity	Isolex (N = 11), n (%)	CliniMACS (N = 32), n (%)
Skin stage		
1	2 (18)	11 (34)
2	1 (9)	7 (22)
3	8 (73)	14 (44)
4	0	0
aGVHD grade		
I	2 (18)	8 (25)
II	1 (9)	8 (25)
III	7 (64)	13 (41)
IV	1 (9)	3 (9)

patients receiving traditional T cell- replete transplantations, producing only limited data on markers that might aid clinicians in the early diagnosis of aGVHD after CD34$^+$-selected allo-HSCT [23]. In this study, we aimed to assess the etiology of acute rash after CD34$^+$-selected allo-HSCT and the evaluate the utility of bedside or laboratory markers in distinguishing cutaneous aGVHD rash from non-aGVHD rash.

Conditioning intensity, use of total body irradiation, female donor to male recipient, and graft source have been previously shown to affect the risk of developing aGVHD after T cell-replete allo-HSCT [24,25]. In our study of CD34$^+$-selected grafts, donor sex, patient sex, or HLA match were not associated with the diagnosis of cutaneous aGVHD rash versus non-aGVHD rash. Cutaneous aGVHD was less common in the Isolex group compared with the CliniMACS group. Barba et al. [1] previously reported a similarly significantly lower rate of grade II-IV aGVHD with Isolex compared with CliniMACS (HR, .4; $P = .38$). In our study, the incidence of cutaneous aGVHD rash, was statistically significantly lower in the Isolex group compared with the CliniMACS group. The graft content of CD3$^+$ cells after CD34$^+$ selection was statistically significantly lower in the Isolex group, possibly contributing to the higher incidence of cutaneous aGVHD in the CliniMACS group. More than one-half of the patients with cutaneous aGVHD in our study developed stage 3 disease. Delayed diagnosis and management or refractoriness to therapy for aGVHD may have led to a more severe skin presentation in our cohort. None of our patients developed stage 4 cutaneous aGVHD. Most patients were managed with topical corticosteroids or topical tacrolimus alone.

The leading cause of a non-aGVHD rash in our CD34$^+$-selected allo-HSCT recipients with a clear etiology was drug eruption. Patients who undergo allo-HSCT are at an increased risk of developing drug hypersensitivity reactions (eg, exanthematous eruptions, characterized by a morbilliform or maculopapular rash), as well as drug toxicity reactions (eg, toxic erythema of chemotherapy) with intertriginous prominence and acral erythema [2,26-30]. Cytotoxic agents and antibiotics are common culprits of drug rash in allo-HSCT recipients [2,26]. In our CD34$^+$-selected allo-HSCT population, in addition to cytotoxic agents and antibiotics, keratinocyte growth factor and recombinant glycosylated human IL-7 were common culprits, possibly reflecting institutional standards and protocols in place during the time period examined.

Pruritus is commonly associated with drug rash but is also frequent in aGVHD [2,31]. In addition, dermatographism may be seen in drug reactions and in allo-HSCT recipients [26]. In our cohort of CD34$^+$-selected allo-HSCT recipients, 51% of cutaneous aGVHD rashes and 63% of non-aGVHD rashes were associated with pruritus; however, this difference was not statistically significant. In a study of T cell-replete allo-HSCT recipients, Byun et al. [2] similarly found no significant difference in pruritus between GVHD and drug rash groups.

Peripheral eosinophilia is part of the diagnostic criteria for systemic drug rashes (DRESS) and is a common feature in drug hypersensitivity reactions [11]. Consequently, elevated eosinophil counts are frequently used by physicians to favor a drug eruption over cutaneous aGVHD [7,32]. However, eosinophilia is also observed more frequently in patients with aGVHD than in those without aGVHD [33]. In studies of patients undergoing T cell-replete allo-HSCT, the incidence of eosinophilia was not significantly different between patients with drug eruptions and those with cutaneous aGVHD [9,32]. Similarly, in our analysis, we found a median percentage of peripheral eosinophils of 2% in both cutaneous aGVHD and non-aGVHD rashes, and only 11% of patients in each rash group had elevated percent eosinophilia. Owing to a lack of corresponding skin biopsies in our cohort of CD34$^+$-selected allo-HSCT recipients, we were unable to evaluate for tissue eosinophilia. Notably, Fischer et al. [5,34] reported a higher frequency of dermal eosinophils in CD34$^+$-selected cutaneous aGVHD (31% versus 3%) and non-aGVHD (65% versus 5%) rash biopsies when compared with those of T cell-replete allo-HSCT recipients. These results suggest that tissue eosinophils may play a greater role in CD34$^+$-selected allo-HSCT recipients than in T cell-replete allo-HSCT recipients irrespective of the development of aGVHD; however, peripheral eosinophils may have only limited value in differentiating cutaneous aGVHD rash and non-aGVHD rash.

Biopsies of rashes in CD34$^+$-selected and T cell-replete allo-HSCT recipients show histological differences. Cutaneous aGVHD biopsies following CD34$^+$-selected allo-HSCT more frequently demonstrate adnexal involvement, satellitosis, lymphocytic exocytosis, epidermal acanthosis, and dermal melanophages, neutrophils, plasma cells, and eosinophils [5]. CD34$^+$-selected non-aGVHD rashes also have higher levels of inflammatory infiltrates [5]. Drug hypersensitivity rashes are classically characterized by epidermal spongiosis, vacuolar changes, and dermal perivascular lymphocytic infiltrates with eosinophils [26]. Toxic erythema of chemotherapy presents with histological atypia, keratinocyte apoptosis, bizarre mitotic configurations and arrest, basal vacuolar degeneration, dermal edema, and eccrine squamous syringometaplasia; however, these changes may be incidentally seen in patients with recent chemotherapy and concurrent unrelated rash [29]. Despite these differences, the utility of biopsies to distinguish cutaneous aGVHD from non-aGVHD rashes, such as drug hypersensitivities, continues to be debated [8-10,35,36]. Our study revealed that the majority of patients who had a final clinical diagnosis of drug rash had skin biopsies with signs of a drug rash (73%); however, 25% of skin biopsies had evidence of both drug rash and GVHD, limiting the dermatopathologist's ability to assign a diagnosis. As such, clinical course, including discontinuation of potential drug culprits, development of extracutaneous GVHD, and response to immunosuppressive therapies, is essential to establish the appropriate diagnosis. Although a skin biopsy may be unable to unequivocally differentiate drug reactions from cutaneous aGVHD, biopsies can still be useful in allo-HSCT recipients when diagnosing an atypical presentation of infection or toxic erythema of chemotherapy, as well as for documenting severity of disease over time [7].

New correlates to confirm the diagnosis of cutaneous aGVHD that do not rely on a skin biopsy or traditional laboratory data have been proposed. A promising biomarker for the differentiation of cutaneous aGVHD rash from drug

hypersensitivity rash is elafin [36,37]. Paczesny et al. [37] found overexpression of elafin in 70% of skin biopsies from patients with cutaneous aGVHD but in none of those with non-aGVHD drug rashes. However, a recent study of 49 hospitalized patients with cancer revealed elevated serum elafin levels in both severe drug rashes (severe cutaneous adverse reactions) and in cutaneous aGVHD. As such, blood elafin is not a useful biomarker for differentiate between cutaneous aGVHD and drug rashes in cancer patients [38].

Our study has several limitations. Patient data were collected at a single center, which might affect the generalizability of results. Although the data were collected over a 3-year period, the sample size was small and was further restricted when stratified by method of $CD34^+$ selection. To better assess rash in $CD34^+$-selected allo-HSCT recipients, a future prospective study to allow for a standardized collection of rash characteristics, as well as serum and tissue correlates, is needed. Despite these challenges, our analysis highlights the frequency of drugs as a cause of rash, as well as the limitation of pruritus and eosinophilia in the differentiation and diagnosis of aGVHD and non-aGVHD skin rash in $CD34^+$-selected allo-HSCT recipients.

CONCLUSIONS

In our case series of 243 $CD34^+$-selected PBSCT recipients, of whom 152 had rash, more than three-quarters of all non-aGVHD rashes with clear etiologies were attributed to drugs. Acute rash in patients who received a $CD34^+$-selected graft via Isolex was more often due to a drug effect, whereas a higher proportion of acute rashes after CliniMACS were due to cutaneous aGVHD. Our results suggest that the commonly used feature of peripheral eosinophilia might not be helpful in differentiating between aGVHD rash and drug rash after $CD34^+$-selected allo-HSCT. Similarly, the proportion of patients with pruritus at rash onset was not different between those with rash due to cutaneous aGVHD and those with non-aGVHD rash after $CD34^+$-selected allo-HSCT. If the clinical scenario supports the diagnosis of a rash as aGVHD-related, the presence of peripheral eosinophilia or pruritus should not delay the initiation of therapy for aGVHD. Of those patients receiving $CD34^+$-selected grafts who developed cutaneous aGVHD, a larger proportion had been processed with CliniMACS compared with Isolex.

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