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The Anatomic Distribution of Skin Involvement in Patients with Incident Chronic Graft-versus-Host Disease

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A B S T R A C T

Little is known about the anatomic distribution of cutaneous chronic graft-versus-host disease (cGVHD). Using data from the cGVHD Consortium Improving Outcomes Assessment Study, we describe the frequency and extent of erythema and superficial and deep sclerosis in 8 anatomic sites in patients with incident disease (ie, new cGVHD diagnosis within 3 months of study entry) receiving systemic therapy. Of 339 patients with incident disease, 182 (54%) had skin involvement. When an extremity was involved, the same type of disease was present contralaterally in 92% of cases, revealing a high level of symmetry. As anticipated, erythema was the most common incident feature; however, sclerotic skin involvement at the time of cGVHD diagnosis was more common than has been suggested by previous studies. Erythema occurred in 155 (85%) and sclerosis in 53 (29%) of the patients with skin involvement (46% and 16%, respectively, of the entire cohort of 339 incident cGVHD cases). Erythema was least common on the lower extremities (n = 71; 39% of patients with skin involvement). Moveable sclerosis was rare on the head, neck, and scalp (n = 4; 2%). Deep sclerosis did not occur in this region, and instead was most likely to occur on the upper extremities (n = 14; 8%) and lower extremities (n = 14; 8%). More than one-half of patients with erythema (n = 107; 58.7%) had diffuse involvement (4 or more of 8 sites involved), compared with less than one-third of those with sclerosis (n = 16; 30.2%).

INTRODUCTION

Skin is the most common area of chronic graft-versus-host disease (cGVHD) involvement, and classic skin features of cGVHD are sufficient to establish the diagnosis [1]. However, little is known about the distribution of cutaneous cGVHD. Studies detailing the anatomic distribution of cGVHD skin involvement are limited, although the incidence and risk factors have been well described [2,3]. Understanding the distribution and symmetry of cGVHD is essential to establish target or sentinel areas (if any) on which to focus monitoring efforts in future studies.

The largest study examining cutaneous cGVHD distribution reported to date is a retrospective study conducted in Korea of 100 patients [4], in which 26% had whole-body erythema, defined as involvement of all anatomic regions, but not requiring 100% body surface area (BSA) involvement. A review of 10 patients with cutaneous sclerotic cGVHD reported frequent involvement of the trunk and extremities [5]. In another series of 17 patients, 70% had generalized sclerosis, which commonly began on the trunk and spread to the extremities [6]. Sclerotic cGVHD has been noted to localize to sites of injury as an isomorphic response [7]. Note that none of the aforementioned studies specifically studied incident disease.

Our aim in the present study was to characterize the anatomic distribution (frequency and extent of sites, as well as symmetry) in incident patients enrolled in the cGVHD Consortium [8]. According to the definitions and enrollment criteria for this prospective multicenter study, all of these patients were within 3 months of diagnosis of cGVHD and receiving systemic therapy.

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Skin data collected in large studies of cGVHD must be interpreted with the understanding that National Institutes of Health (NIH) consensus forms (NIH 2005 [9] and 2014 [1] criteria; Appendix 1 and Appendix 2), cGVHD Consortium forms [8], and other standard instruments depart from typical descriptive dermatologic terminology. (These NIH Consensus forms also can be accessed at https://www.asbmt.org/practice-resources/nih-chronic-gvhd-consensus-project). In particular, cutaneous manifestations of cGVHD generally have been categorized for assessment as sclerotic changes (ie, dermal or subcutaneous involvement) versus "erythematous rash" (ie, epidermal involvement) [10]. Sclerotic features include deep sclerotic features, such as nonmoveable sclerosis and fasciitis, and superficial sclerosis, including morphea-like superficial sclerosis and lichen sclerosus-like papules and plaques [10]. Beyond the traditional dermatologic meaning, the term "erythematous rash" has been defined in cGVHD studies to include "any cutaneous manifestations other than sclerosis" [11] and is variably referred to as "erythematous rash," "erythematous changes," "skin erythema," or "erythema" [12]. In particular, in the 2005 NIH criteria, "erythema" included all epidermal changes, including lichen planus-like eruptions (while avoiding the histopathological term "lichenoid"), maculopapular eruptions, erythroderma, keratosis pilaris, papulosquamous features, ichthyosis, and poikiloderma [10,11]. The 2005 criteria also recommended recording the extent of other cGVHD pigmentary changes, including hypopigmentation and hyperpigmentation, which are not necessarily reflective of current active disease [9,10]. An example of a potential source of confusion is the very common presentation of "erythematous" cGVHD mimicking lichen planus, which is actually more violaceous than erythematous and would not be considered a typical erythematous eruption in the field of dermatology.

The diagnosis and classification of cutaneous involvement in cGVHD is complex and has changed over time. cGVHD includes both classic cGVHD and overlap cGVHD, which contains features of both acute GVHD (aGVHD) and chronic disease [9]. The original definition of cGVHD was any manifestation of GVHD occurring at least 100 days after allogenic stem cell transplantation (allo-SCT) [9]. This definition changed with the NIH 2005 consensus criteria for a diagnosis of cGVHD, which included either a diagnostic clinical manifestation of cGVHD or a distinctive manifestation with biopsy-proven cGVHD; for example, either poikiloderma or a sclerotic feature alone is considered diagnostic of cGVHD [9]. The 2005 criteria also introduced an overall composite score for skin severity ranging from 0 (no involvement) to 3 (most involvement). This score is based on combined BSA involvement using the "rule of 9s" for total BSA estimation and degree of sclerosis severity. Importantly, the "rule of 9s" is used not when clinically evaluating skin features, but later when tallying the results of the clinical assessment (Appendices 1 and 2) [9]. By the 2005 NIH criteria, all cutaneous changes, including "diagnostic" (eg, poikiloderma, lichen planus-like, sclerotic, morphea-like, lichen sclerosus-like features), "distinctive" (eg, depigmentation, scaling papulosquamous lesions), "common" (eg, erythema, maculopapular rash, pruritus), and "other features" (eg, sweat impairment, ichthyosis, keratosis pilaris, hypopigmentation, hyperpigmentation) are scored as BSA involvement for the NIH Skin Score, except for sweat impairment [9]. Note that clinicians did not strictly adhere to these guidelines in the cGVHD Consortium study which provided the source of our data. In particular, study clinicians likely did not include hypopigmentation and hyperpigmentation in BSA scoring and in fact were not asked to record the presence or absence of pigmentation disorders (Appendix 3). Pigmentary changes are a significant source of variation and confusion in cGVHD assessment. General opinion has shifted to avoiding them in the years following the 2005 criteria, because they often reflect burnt-out and not active disease.

After the data we report here had been collected, the scoring of cutaneous cGVHD changed formally with the updated NIH 2014 consensus criteria. The 2014 criteria skin score consists of a score of 0 to 3, based solely on BSA involvement and a score of 0, 2, or 3, based on the presence of superficial or deep sclerosis. The higher of these 2 scores is the overall skin score [1]. In contrast to the 2005 criteria, the 2014 criteria do not include areas with pigmentary changes alone, such as poikiloderma (even though it is still considered diagnostic) and hypopigmentation or hyperpigmentation, in the calculation of affected BSA [1,10].

Alternative skin scoring systems have been created for cGVHD, including the Vienna Skin Score, which uniquely captures hypopigmentation and hyperpigmentation, and the Hopkins Scores for sclerosis and fascia involvement (Appendix 3), which do not evaluate epidermal involvement [13,14].

METHODS

Study Design

Research was conducted with patient informed consent and Institutional Review Board approval, in accordance with the Declaration of Helsinki. Clinical data were analyzed from patients with incident cGVHD (ie, development of disease within 3 months after the first study visit) enrolled in the cGVHD Consortium Improving Outcomes Assessment Study [8], a prospective multicenter observational study designed to document the natural history of cGVHD. This study collects extensive data on patients with cGVHD, with providers completing an 8-page form at patient enrollment. The study forms and data collection methods have been described previously [8]. Patients who had a clinical diagnosis of cGVHD by their transplantation physician and were receiving systemic therapy were eligible. Baseline data were used. GVHD subtype was recorded prospectively by study clinicians using the NIH 2005 consensus criteria to differentiate late-onset aGVHD, classic cGVHD, and overlap aGVHD and cGVHD [9]. Patients with late aGVHD were included, using the original definition of cGVHD, based on timing after allo-SCT ($\geq$100 days) and literature supporting the inclusion of these patients in cGVHD clinical trials [15]. This cohort has been used previously to validate the NIH Skin Score [11].

A total of 339 adult patients met the inclusion criteria of incident cGVHD and NIH organ scores recorded in all domains. Of these, 133 patients with an NIH Skin Score of 0 and no BSA involvement, 14 patients with an NIH Skin Score of 0 and BSA involvement, and 24 patients with an NIH Skin Score $>$0 without marked BSA involvement were excluded. Both of these latter exclusions reflect errors in data collection based on the assessment criteria. After these exclusions, 182 patients were included in the analysis of cutaneous disease distribution.

Skin Scoring

Skin scores at enrollment were analyzed. The clinicians who performed skin scoring were predominantly hematologist-oncologists and advance practice practitioners with subspecialization in stem cell transplantation, some with additional cGVHD expertise.

A standardized template was used to document the distribution and extent of skin involvement based on a form adapted from the 2005 NIH consensus criteria (Appendix 1) [9]. Only changes known or suspected to be related to cGVHD

were to be documented. The percentage of an anatomic region with skin involvement was determined in 3 domains: erythema, moveable sclerosis, and nonmoveable subcutaneous sclerosis or fasciitis, referred to as deep sclerotic features [10]. Of note, for erythema, some clinicians might have scored hypopigmentation and hyperpigmentation based on the 2005 NIH criteria; however, most likely very few clinicians scored these features, in anticipation of the 2014 criteria. The term "moveable sclerosis" includes lichen sclerosus-like, morphea-like, and generalized superficial sclerosis. Within "deep sclerosis," the term "hidebound sclerosis" is used to describe subcutaneous sclerosis that is so severe that the skin cannot be moved relative to underlying tendons and fascia [9,16]. Deep sclerosis also includes other signs of deeper involvement, such as a "groove sign," when involvement of muscle fascia causes rippling of the overlying skin.

The 2005 NIH criteria for skin assessment included 8 anatomic regions: head/neck/scalp, anterior torso, posterior torso, left upper extremity, right upper extremity, left lower extremity, right lower extremity, and genitalia [10]. If the genitalia are not examined, this is documented [10]. It is possible to have all 3 types of involvement (erythema, superficial, and deep sclerosis) simultaneously; therefore, total BSA can be a maximum of 300% when all 3 types of involvement are combined. This assessment is part of the standard for cGVHD staging in clinical trials [9] and since has been applied to standard clinical practice; however, no study-specific training was provided to clinicians. BSA calculations are described below.

Clinicians also recorded 2005 NIH composite skin scores from 0 to 3 (Appendix 2) [9]. The presence of skin features (eg, lichen planus or maculopapular rash) was also recorded for a subset of the possible features specified by the 2005 NIH criteria. Notably, the study form did not include hypopigmentation, hyperpigmentation, or sclerosis. However, sclerosis was accounted for in BSA calculations, as were hypopigmentation and hyperpigmentation in some cases (Appendix 4). Additional characterization of sclerosis was recorded using Hopkins Scores (Appendix 3) [14].

In summary, the following tools were used to document skin features in this cohort of patients:

- Percentage of anatomic region involved using a form adapted from the NIH 2005 consensus criteria (Appendix 1) [9,10]
- NIH 2005 Skin Scores from 0 to 3 (Appendix 2) [9]
- Hopkins Sclerosis and Fascia Scores (Appendix 3) [14]
- Clinical skin features form, including only a subset of features in the 2005 NIH consensus criteria (Appendix 4) [9]
- Vienna Skin Score (not included in this analysis) [13].

Statistical Analysis

Analyses were performed using Stata 14.2 for MacOS (StataCorp, College Station, TX). Data were recorded by clinicians as the percentage of an anatomic region involved (Appendix 1). The "rule of 9s" [17] was then applied during analysis to estimate BSA involvement at each anatomic region in the 3 domains described above (even though the clinicians were asked not to use the "rule of 9s" during data collection) [11]. We defined combined involvement as the presence of both erythema and sclerosis. Diffuse skin involvement was defined a priori as involvement in >50% of the sites (ie, 4 or more). An area was considered to have skin involvement if >0% was involved. The number of areas with involvement were counted.

The 8 anatomic sites were grouped for analysis into 5 regions: head/neck/scalp, anterior torso, posterior torso, upper extremities, and lower extremities. Specifically, data on the right and left upper extremities were collected individually but combined for some analyses, and the same was done for the lower extremities. The genitalia were excluded from comparisons between regions, because the genitalia were not examined in 65 patients (35.7%). The genitalia were included in other descriptive analyses. McNemar's test was used to compare the proportion of patients with skin involvement in 1 region versus another, such as the likelihood of erythema of the anterior torso versus the posterior torso. All permutations of pairwise comparisons among 2 of the 5 regions were compared (10 comparisons), and an α of .005 was considered statistically significant, based on a Bonferroni correction for multiple comparisons. Anatomic regions divided into specific sides of the body (ie, the right and left upper and lower extremities) were compared for symmetry. For this analysis, the right and left upper extremities were assigned as either the more involved or less involved extremity, based on the percentage of involvement, and were compared using a 2-sided paired *t*-test. This was also done for comparison between the right and left lower extremities. The percentage of patients with bilateral extremity involvement across upper versus lower involvement and type of skin involvement was averaged using an unweighted average. Continuous variables are reported as mean ± SD or median (interquartile range [IQR]), and categorical variables are reported as number (%).

RESULTS

Patient and Cutaneous Characteristics

Patient characteristics and cutaneous cGVHD features of the 182 analyzed incident cases with skin disease (ie, patients with new diagnosis of cGVHD within 3 months of study enrollment) are summarized in Tables 1 to 3. Among the 182 patients, 110 (60%) had classic cGVHD, 64 (35%) had aGVHD and cGVHD, and 8 (4%) had late aGVHD. All patients were receiving systemic therapy according to the enrollment criteria for this cGVHD Consortium study.

Erythema was the most common manifestation, present in 155 patients (85.2%) with skin disease. A higher proportion of patients had erythema than had sclerotic features ($P < .0001$), and moveable sclerosis was more common than deep sclerotic features ($P = .01$). Fifty-three patients (29.1%) had any type of sclerosis, including 42 (23.1%) with moveable sclerosis and 26 (14.3%) with deep features. Among the 42 patients with moveable sclerosis, 15 (35.7%) also had deep features, and among the 26 patients with deep features, 15 (57.7%) also had moveable sclerosis. Among the original cohort of 339 patients, 155 (45.7%) had erythema and 53 (15.6%) had sclerosis at the time of incident cGVHD.

Skin features are described in Table 2. Maculopapular rash was the most common, followed by lichen planus-like lesions, correlating with the high percentage of patients with documented erythema. The least common feature was an ulcer. The mean number of skin features was 1.5 ± 1.2, with 78 (42.9%) of the cohort having more than 1 feature; 6 patients (3.3%) had 5 features. Thirty-seven patients (20.3%) with skin disease did not have documented skin features. Because sclerosis is not on the list of skin features in the Clinical Skin Features Scoring Sheet (Appendix 4), we repeated the analysis, considering sclerosis or fasciitis noted elsewhere on the data collection form as an additional feature. In this reanalysis, the number of patients without any documented skin features decreased to 16 (8.8%)

Table 1
Patient and Transplantation Characteristics at cGVHD Diagnosis (Study Entry) in Patients with Cutaneous cGVHD Involvement (N = 182)

Characteristic	Value
Age, yr, mean ± SD	50.7 ± 13.0
Male sex, n (%)	112 (61.5)
Race, n (%)	
Caucasian	172 (94.5)
Asian	4 (2.2)
African American	3 (1.7)
Other	3 (1.7)
Disease type, n (%)	
Acute leukemia	84 (46.2)
Myeloid disorder	31 (17.0)
Lymphoid disorder	55 (30.2)
Other malignant*	9 (4.9)
Other nonmalignant†	3 (1.6)
Disease status before transplantation, n (%)‡	
Early	68 (37.4)
Intermediate	71 (39.0)
Advanced	43 (23.6)
Donor match, n (%)	
HLA-identical sibling	70 (38.5)
Other related	7 (3.8)
Well-matched unrelated	79 (43.4)
Partially matched unrelated	26 (14.3)
NIH Overall Severity Score, n (%)	
Mild	12 (6.6)
Intermediate	74 (40.7)
High	96 (52.8)
cGVHD subtype, n (%)	
Classic cGVHD	110 (60.4)
Overlap aGVHD and cGVHD	64 (35.2)
Late aGVHD§	8 (4.4)
Previous aGVHD (grade II-IV only), %	
Noncutaneous areas of cGVHD involvement (NIH Score >0), n (%)	96 (52.8)
Mouth	109 (59.9)
Gastrointestinal	60 (33.0)
Eye	73 (40.1)
Joints	45 (24.7)
Genital tract	16 (8.8)
Lung	26 (14.3)

* Includes multiple myeloma (n = 9) and plasma cell leukemia (n = 1).
† Includes aplastic anemia (n = 2) and paroxysmal nocturnal hemoglobinuria (n = 1).
‡ Defined as early, intermediate and advanced using the CIBMTR classification [27].
§ Eight patients with late aGVHD were included based on the original definition of cGVHD based on timing after allo-SCT (≥100 days) and literature supporting the inclusion of these patients in cGVHD clinical trials [15].

of those with skin findings. Eleven patients (6.0%) had erythroderma, defined as erythema involving at least 90% of BSA.

Anatomic Distribution of Skin Involvement

The distribution of skin involvement stratified by anatomic region and type of involvement is shown in Table 4. For this analysis, statistical comparisons between the proportion of patients with involvement in a given region are provided for erythema in Supplementary Table 1, for moveable sclerosis in Supplementary Table 2, and for deep sclerotic features in Supplementary Table 3. The median percentage of skin involvement in each anatomic region with involvement is shown in Table 4.

For erythema, the anterior torso was more likely than the posterior torso to have involvement (116 [63.7%] versus 99 [54.4%]; $P = .003$; Supplementary Table 1). Only 71 patients (39.0%) had lower extremity erythema; this region was less likely to have erythema than any other area ($P < .001$). Moveable sclerosis was more homogenous; the head/neck/scalp had less involvement than with the anterior torso and extremities

Table 2
Descriptive Statistics for Skin Features in the Patients with cGVHD and Cutaneous Involvement (N = 182)

Skin Feature	Value*,†
Patients with involvement, n (%)	
Erythema	155 (85.2)
Any type of sclerosis#	53 (29.1)
Moveable sclerosis	42 (23.1)
Deep sclerotic features	26 (14.3)
Both moveable and deep sclerosis	15 (8.2)
Combined erythema and sclerosis	26 (14.3)
Average BSA involvement, mean ± SD	
Erythema	27.0 ± 29.6
Moveable sclerosis	2.13 ± 5.55
Deep sclerotic features	1.60 ± 6.37
Skin features, n (%)†	
Ulcer	5 (2.8)
Keratosis pilaris	9 (5.0)
Maculopapular rash	97 (53.3)
Lichen planus-like lesions	43 (23.6)
Papulosquamous lesions or ichthyosis	12 (6.6)
Poikiloderma	6 (3.3)
Pruritus	33 (18.1)
Hair involvement	15 (8.2)
Nail involvement	23 (12.6)
Other skin features	31 (17.0)

* Patients can be counted twice, so values do not add up to 100%. For example, a patient may fit into all 4 categories: moveable sclerosis, deep sclerotic features, both moveable and deep sclerosis, and combined erythema and sclerosis.
† Skin features that contribute to the category "erythematous rash of any sort" are in italics. This reflects NIH 2005 criteria [10].

($P < .005$; Supplementary Table 2). Other regions did not differ statistically from one another in terms of sclerotic involvement. Deep sclerotic features were more likely seen on the extremities compared with all other regions ($P < .005$; Supplementary Table 3). Notably, upper extremity and lower extremity involvement did not differ significantly for either moveable or deep sclerosis.

Bilateral Symmetry

As shown in Table 5, there was significant symmetry between the right upper extremities and left upper extremities. The same was true for the lower extremities. When interpreting the data in Table 5, it is important to note that a single patient's upper extremities could be counted up to 3 times, by

Table 3
NIH and Hopkins Skin Scores for Our Cohort

Score	Score Definition	cGVHD Patients (N = 182), n (%)
NIH 2005 Skin Score*		
1	<18% of BSA with disease signs but no sclerotic features	54 (29.7)
2	15%-19% of BSA or superficial sclerotic features	65 (35.7)
3	>50% of BSA or deep sclerotic or impaired mobility, ulceration, or severe pruritus	63 (34.6)
Hopkins Sclerosis Score*		
0	Normal	135 (74.2)
1	Thickened with pockets of normal skin	32 (17.6)
2	Thickened over majority of skin	5 (2.8)
3	Thickened unable to move	3 (1.7)
4	Hidebound, unable to pinch	7 (3.9)
Hopkins Fascia Score*		
0	Normal	146 (80.2)
1	Tight with normal areas	23 (12.6)
2	Tight	9 (5.0)
3	Tight, unable to move	4 (2.2)

* Scoring systems described by Filipovich et al [9] and Inamoto et al [14].

Table 4
Patients with Skin Involvement at the 8 Anatomic Sites and Percentage of Anatomic Area Involved

Area of Involvement	Erythema, n (%)	% Erythema, median (IQR)	Moveable Sclerosis, n (%)	% Moveable Sclerosis, median (IQR)	Deep Sclerotic Features, n (%)	% Deep Sclerotic Features, median (IQR)	Any Type of Sclerosis, n (%)	Any Type of Skin Involvement, n (%)
Head/neck/scalp	99 (54.4)	50 (25-90)	4 (2.2)	35 (13-63)	0 (0)	–	4 (7.6)	101 (55.5)
Anterior torso	116 (63.7)	68 (25-100)	15 (8.2)	25 (10-50)	1 (.5)	–	16 (30.2)	125 (68.7)
Posterior torso	99 (54.4)	75 (25-100)	11 (6.0)	25 (20-50)	3 (1.6)	–	14 (26.4)	108 (59.3)
Left upper extremity	98 (53.8)	50 (25-80)	18 (9.9)	20 (10-30)	13 (7.1)	30 (10-50)	27 (50.9)	116 (63.7)
Right upper extremity	97 (53.3)	50 (25-80)	18 (9.9)	20 (10-30)	14 (7.7)	23 (5-45)	27 (50.9)	116 (63.7)
Left lower extremity	68 (37.4)	50 (10-75)	18 (9.9)	20 (5-25)	14 (7.7)	30 (25-50)	27 (50.9)	85 (46.7)
Right lower extremity	69 (37.9)	50 (10-75)	19 (10.4)	20 (10-30)	15 (8.2)	25 (10-50)	29 (54.7)	88 (48.4)
Genitalia*	14 (12.0)	100 (10-100)	1 (.9)	–	0 (0)	–	1 (1.9)	14 (12.0)
All areas†	155 (85.2)	22 (5-53)	42 (23.1)	8 (2-16)	26 (14.3)	6 (1-17)	53 (29.1)	182 (100.0)

Values are shown as n (%) of total cohort with type of skin involvement and as median (IQR) percentage of an area with involvement. The value of skin involvement is calculated only in patients with skin involvement in the region of calculation. The value of skin involvement represents the percentage of the area with involvement, not BSA contributed by the area.

* The denominator for genitalia percentages is based on the total number of patients for whom the genitalia were examined (n = 117).

† The percentage of skin involvement in the all areas category this represents the median (IQR) of total BSA with involvement among the subset of patients affected by erythema (155 patients), moveable sclerosis (42 patients), or deep sclerosis (26 patients).

contributing to each disease domain (erythema, deep sclerosis, and superficial sclerosis). When averaged across all 6 patterns of extremity involvement (3 types of disease for upper extremities and the same 3 types for lower extremities), involvement was bilateral in 88% of the cases (range, 13 to 96; 76.2% to 97.0%) (Table 5). Five of the 6 patterns of extremity involvement had at least 89.5% of patients with bilateral involvement (Table 5), the exception being lower extremity moveable sclerosis, with 76.2% bilaterality. In total, among the 182 patients with incident cutaneous cGVHD, there were 240 instances of an affected extremity pattern, 221 (92%) of which had bilateral involvement.

Number of Anatomic Sites

In patients with erythema, the mean number of involved sites was 4.6 ± 2.4, and the median number was 5 (IQR, 2 to 7) (Figure 1). Diffuse involvement (ie, 4 or more of 8 sites involved) was seen in 107 patients (58.7%). In patients with sclerosis (n = 53), the mean number of sites was 2.7 ± 1.3, and the median number was 2 (IQR, 2 to 4) (Figure 2), with only 16 patients (30.2%) meeting our definition of diffuse involvement.

DISCUSSION

To our knowledge, this is the largest focused analysis of the anatomic distribution of incident cutaneous cGVHD reported to date. Of note, all patients were receiving systemic therapy in accordance with the enrollment criteria of the cGVHD Consortium Improving Outcomes Assessment Study. Thus, these results might not apply to patients with cutaneous cGVHD who do not require systemic therapy. In addition, none of the patients in this cohort received a cord blood transplantation, so these results may not apply to patients receiving this type of SCT [18].

Sclerosis was seen in 53 patients (15.6%) out of the total cohort of 339 patients with incident disease, that is, 29.1% of the 182 patients with cutaneous cGVHD. This suggests that skin sclerosis in patients with newly diagnosed cGVHD may be more common than previously appreciated. Specifically, a large retrospective study reported that 70 of 977 patients (7%) with cGVHD in any organ system had skin sclerosis at the time of diagnosis [2]. The estimated incidence of sclerosis in our study may be higher because of selection bias for more severe cGVHD. This was expected, because our estimates are derived from a natural history study in which systemic therapy was a prerequisite for enrollment [8].

Our findings highlight the potential intensity of incident cutaneous cGVHD. Patients had a high number of skin features and more than one-half of patients with erythema had diffuse disease, defined as 4 or more sites involved. In addition, 16 patients (30.2%) with sclerosis had diffuse involvement. Both of these findings highlight the importance of a total body skin examination when evaluating cGVHD. For example, if cutaneous cGVHD is seen in 1 area, there is a strong possibility of cutaneous involvement elsewhere, even diffuse involvement, and the patient should be carefully examined. The trunk and legs are particularly common areas of involvement and may be missed without complete examination.

Skin involvement in some of the patients in this study has been described in combination with patients with prevalent cases of cGVHD, meaning that diagnosis occurred at any time before study enrollment [11]. The reason for differences in the cohort between this analysis and the previous analysis is that the previous analysis is an older study, so additional subjects were included in our cohort. Importantly, the previous analysis did not distinguish between patients with incident disease versus prevalent disease [11]. When we analyzed patients from

Table 5
Bilaterality Analysis Shown as Number of Patients with Extremity Involvement

Parameter	cGVHD Patients, n (%)	Absolute Value of Right-Left Difference in % of Each Extremity Involved, mean ± SD	*P* Value*
Upper extremity erythema			
Any involvement	99 (100.0)	1.26 ± 6.44	.054
One extremity	3 (3.0)	23.37 ± 25.12	NS
Bilateral involvement	96 (97.0)	.57 ± 3.69	NS
Lower extremity erythema			
Any involvement	71 (100.0)	.33 ± 1.45	.063
One extremity	5 (7.0)	3.62 ± 4.01	NS
Bilateral involvement	66 (92.7)	.08 ± .62	NS
Upper extremity moveable sclerosis			
Any involvement	19 (100.0)	.89 ± 2.51	NS
One extremity	2 (10.5)	6.0 ± 5.66	NS
Bilateral involvement	17 (89.5)	.29 ± 1.21	NS
Lower extremity moveable sclerosis			
Any involvement	21 (100.0)	3.64 ± 7.65	.04
One extremity	5 (23.8)	11.3 ± 12.4	NS
Bilateral involvement	16 (76.2)	1.25 ± 3.42	NS
Upper extremity deep sclerotic features			
Any involvement	14 (100.0)	4.79 ± 13.61	NS
One extremity	1 (7.1)	-	-
Bilateral involvement	13 (92.9)	5.00 ± 14.14	NS
Lower extremity deep sclerotic features			
Any involvement	16 (100.0)	3.44 ± 6.76	.06
One extremity	3 (18.8)	6.67 ± 2.89	.057
Bilateral involvement	13 (81.3)	2.69 ± 7.25	NS

P values >.10 are reported as not significant (NS).
* Comparison of the most involved extremity with the least involved extremity by a 2-sided paired *t* test.

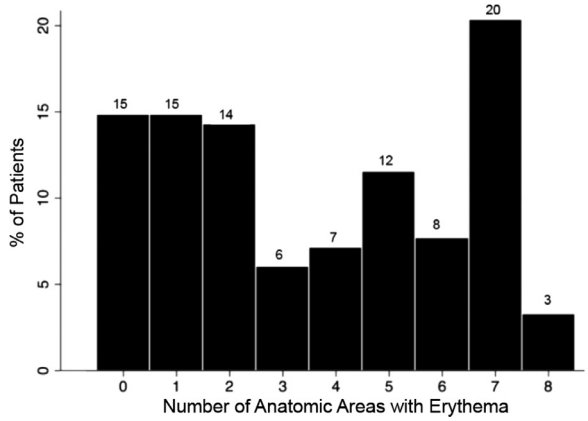

Figure 1. Anatomic areas of erythema. The histogram depicts the percentage of patients with a given number of anatomic sites with erythema, ranging from 0 to 8 sites of involvement. Values on the top of the bars indicate the percentage of patients with the number of anatomic areas of involvement.

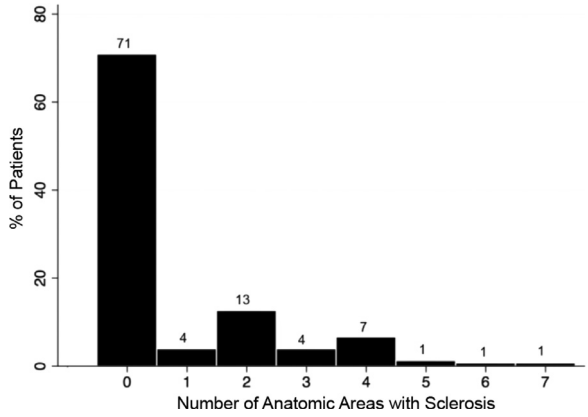

Figure 2. Anatomic areas with sclerosis. The histogram depicts the percentage of patients with a given number of anatomic sites with sclerotic involvement, ranging from 0 to 8 sites of involvement. Values on the top of the bars indicate the percentage of patients with the number of anatomic areas of involvement.

the cGVHD Consortium Improving Outcomes Assessment Study with prevalent cGVHD, 126 of 241 patients (52.3%) had skin involvement based on the criteria defined (BSA involvement and NIH Skin Score >0). Thus, prevalent cases and incident cases had similar rates of cutaneous findings (52.3% versus 53.7%). Of the 126 patients with prevalent cGVHD and cutaneous involvement, 76 (60.3%) had erythema and 79 (62.7%) had sclerosis. This is in contrast to the 182 incident patients with skin involvement, in whom erythema was the most common manifestation, seen in 155 patients (85%), with sclerotic features seen in only 53 (29%). These data show that although the rate of cutaneous disease did not increase substantially from incident cases to prevalent cases, the distribution shifted dramatically toward increased sclerosis and decreased erythema.

The most common skin feature in the present study of incident cases was a maculopapular rash, seen in 97 patients (53%). Maculopapular rash is not a distinctive feature of cGVHD, and its frequency is due in part to the large number (n = 72; 39.6%) of our patients falling into the late acute or overlap subtype of cGVHD (the latter sharing features of both aGVHD and cGVHD) [19].

The current understanding is that erythema and lichen planus-like lesions are aspects of acute inflammation with a later, fibrotic phase driven by profibrotic cytokines, promoting collagen deposition and subsequent sclerosis [20]. We found that both the upper and lower extremities were more likely to be involved by deep sclerosis than all other sites (Supplementary Table 3), a markedly different distribution from that of erythema, which was least common on the lower extremities. The

contrasting distribution between sclerotic and erythematous cGVHD suggests differing pathophysiologic mechanisms driving these subtypes. Thus, our findings challenge the current understanding of disease progression from acute inflammation associated with erythema to later fibrosis.

It is possible that, in our cohort, deep sclerotic features were seen more commonly on the extremities because it may be easier for clinicians to detect skin rippling and soft tissue thickening on the extremities. In addition, skin may be less likely to become hidebound (a criterion for deep sclerosis [9]) on the trunk, where there is more adiposity. These potential confounding factors in clinical assessment underscore the need for new methods to assess biomechanical skin properties beyond palpation.

For moveable sclerosis, distribution was uniform with the exception of the head, neck, and scalp (Supplementary Table 2). This may be explained by the lack of tension in this region, leading to a lack of isomorphic response [7]. In contrast to systemic sclerosis, in which facial tightening is common [21], cGVHD sclerosis does not have a predilection for the face [4]. In the extremities, we observed impressive bilateral symmetry of all types of disease involvement (Table 5). Symmetry of skin involvement is seen in many other cutaneous conditions resulting from immune dysregulation, including psoriasis and scleroderma [22,23].

Important limitations of this study include the lack of quality control in the data. The NIH classification system was not developed for dermatology research; for instance, there was no specific training on the definition of a maculopapular rashes, which have a broad differential diagnosis [9]. Clinicians were instructed to only grade skin findings that were known or suspected to be related to cGVHD; however, it is possible that some of the documented skin findings were related to other causes, such as viral exanthems or drug rashes. In addition, it is not possible to determine whether all patients were scored for hypopigmentation and hyperpigmentation. Pigmentary changes were part of the erythema domain in the NIH 2005 criteria that form the basis of the present study, but were excluded from the study data collection forms (Appendices 1 through 4), as well as from the NIH 2014 criteria. Some study clinicians scored these features, but others did not. An example of the potential for errors in the collected data is the fact that 14 patients with an NIH Skin Score of 0 were noted to have BSA involvement and 24 patients with an NIH Skin Score >0 had no BSA involvement. Although these patients were excluded from our analysis, this reflects the inherent error rate in data collection and documentation. Furthermore, study clinicians were not specifically trained on which types of skin involvement to classify as erythema, moveable sclerosis, or nonmoveable sclerosis and fasciitis; therefore, the percent BSA scoring in different domains likely has strong interobserver variation. This variation should be mitigated by the study clinicians' knowledge of the NIH 2005 classification system. In addition, percent BSA estimations historically suffer from inaccuracy and poor interobserver reproducibility [24].

Other caveats to this work include the terminology used, possibility of incomplete examination, and limitations due to inclusion criteria. Incomplete examination could have falsely decreased the observed involvement in some areas, especially for less readily visible areas such as the legs. Furthermore, we report on distribution using only a small number of patients with sclerotic features, and edema can precede sclerosis but was not documented in this study [25]. Notably, an inclusion criterion for enrollment in the cGVHD Consortium Improving Outcomes Assessment Study was receipt of systemic therapy for cGVHD; thus, many cGVHD patients with organ involvement limited to skin or mild cutaneous involvement would not have met this criterion. It is also possible that systemic treatment could have impacted the type and distribution of skin involvement. Finally, this study combines patients with classic cGVHD, overlap cGVHD, and late-onset aGVHD; further studies are needed to determine how these results can be applied to each subtype of cGVHD.

To the best of our knowledge, this is the largest focused analysis of the anatomic distribution of incident cutaneous cGVHD reported to date. Erythema was less common on the lower extremities. Moveable sclerosis was less common on the head/neck/scalp, and deep sclerotic features were most common on the extremities. Each potential anatomic site had documented involvement at the time of cGVHD diagnosis in at least 1 patient, with the exception of deep sclerosis of the genitalia and face. This demonstrates that a total body skin examination is essential in cGVHD assessment. When performing this examination, it is important to bear in mind that the palm, not including the fingers, is equivalent to .5% of total BSA [26]. Another observation was a pronounced right-left symmetry. This detailed characterization of the distribution and symmetry of cGVHD skin involvement can provide insight to develop optimal assessment protocols encompassing the extent of affected areas. This can support the development of biomechanical or imaging devices that measure cutaneous cGVHD, paving the way toward future technological cGVHD assessment.

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Conflict of interest statement: S.J.L. serves as a consultant for Incyte, is on advisory boards for Kadmon and Amgen, and has received speaker honoraria and travel expenses from Mallinckrodt. C.C. is a consultant for Pfizer, Pharmacyclics, Kite, Bristol-Myers Squibb, Incyte, and Astellas. M.F. is a consultant for Pharmacyclics. M.H.J. is a consultant for and has received research funding from Mallinckrodt and Janssen. The other authors declare no conflicts of interest.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.bbmt.2018.09.007.

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