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Risk Factors and Characterization of Vitiligo and Alopecia Areata in Patients With Chronic Graft-vs-Host Disease

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Abstract

IMPORTANCE—Cutaneous manifestations of chronic graft-vs-host disease (GvHD) are highly variable and may recapitulate well-characterized autoimmune diseases, including systemic sclerosis and Sjögren syndrome. However, vitiligo and alopecia areata (AA) have not been well characterized in the chronic GvHD setting.

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OBJECTIVE—To determine laboratory markers, transplant-related factors, and other systemic manifestations associated with vitiligo and/or AA in patients with chronic GvHD.

DESIGN, SETTING, AND PARTICIPANTS—A cross-sectional, retrospective study conducted by the National Institutes of Health (NIH) of 282 adult and pediatric patients with chronic GvHD seen under the NIH natural history protocol between 2004 and 2013.

MAIN OUTCOMES AND MEASURES—Demographic, clinical, and laboratory data, including measures of 11 antibodies, were included in the analysis. Patients with vitiligo and/or AA were identified from dermatologist documentation and photographic evidence. Univariate and multivariable logistic regression analyses were used to determine risk factors for vitiligo and AA development.

RESULTS—Fifteen (5.3%) of 282 patients demonstrated vitiligo (14 of 282; 4.9%) and/or AA (2 of 282; 0.7%) (1 patient had both vitiligo and AA). Univariate analysis identified female donor to male recipient sex mismatch ($P = .003$), positive test results for anticardiolipin (ACA) IgG ($P = .03$) or antiparietal antibody ($P = .049$), elevated CD19 level ($P = .045$), and normal or elevated IgG level ($P = .02$) as risk factors for vitiligo or AA. Female donor to male recipient sex mismatch ($P = .003$) and positive findings for ACA-IgG ($P = .01$) retained significance in the multivariable analysis.

CONCLUSIONS AND RELEVANCE—Female donor and female donor to male recipient sex mismatch, in particular, are significantly associated with the development of vitiligo and/or AA. Further studies are needed to explore transplant-related risk factors that may lead to better understanding of the pathomechanisms of chronic GvHD.

Chronic graft-vs-host disease (GvHD) is one of the most frequent and devastating complications arising after allogeneic hematopoietic stem cell transplantation(HSCT) and is the major cause of mortality and late non–relapse-associated morbidity in long-term survivors.[1] Occurring in up to 80% of allogeneic HSCT recipients,[2] chronic GvHD is a multiorgan disease that is associated with immune dysfunction and often significantly impacts quality of life.[3] The skin is the most commonly affected organ—presentations range from nonsclerotic epidermal involvement (such as lichen planus–like eruptions or poikiloderma) to morphea-like or deep sclerotic disease resembling fasciitis.[4]

The underlying biology of chronic GvHD has not been fully elucidated; however, many of its cutaneous and histologic features recapitulate those of well-characterized autoimmune diseases such as systemic sclerosis and Sjögren syndrome. Other autoimmune manifestations, including autoimmune cytopenias, myasthenia gravis, and autoimmune thyroid diseases, are also increasingly recognized after allogeneic HSCT.[5] Several case reports and small series have reported vitiligo[6–19] or alopecia areata (AA)[18–20] following HSCT, most occurring in the setting of GvHD, further supporting the role of GvHD in the development of cutaneous autoimmune disease.[21] However, the frequency of skin autoimmune manifestations and associated risk factors have not been well described.

In this retrospective cross-sectional analysis, we examine the prevalence of autoantibodies and other risk factors for the development of vitiligo and/or AA in a cohort of 282 patients

with chronic GvHD who were comprehensively evaluated as part of a National Institutes of Health (NIH) chronic GvHD natural history study.

Methods

The study was approved by the institutional review board of the National Cancer Institute, and all participants provided written informed consent.

Patient Population and Chronic GvHD Assessment

A total of 282 adult and pediatric patients with a diagnosis of chronic GvHD, as defined by the NIH Consensus Group Criteria,[22] and referred to the NIH Clinical Center between 2004 and 2013 were included in this cross-sectional analysis (Figure 1). All participants were enrolled in an NIH chronic GvHD natural history protocol (clinicaltrials.gov Identifier: NCT00331968) and were comprehensively evaluated by a multidisciplinary team during a week-long visit in which demographic, clinical, photographic, imaging, and laboratory data were obtained.[23] Comprehensive skin assessment included full body skin examination, body surface area scoring, and skin biopsy.

Participants with vitiligo and/or AA were compared with participants in the cohort with documented chronic GvHD of the skin or other organ system who did not manifest vitiligo or AA. Diagnosis of skin chronic GvHD was determined by NIH Consensus Criteria.[22] Diagnostic skin manifestations included poikiloderma, lichen planus–like eruption, morphea-like superficial sclerotic features, lichen sclerosus (LS)-like lesions, and deep sclerotic features. According to NIH Consensus Criteria, pigmentary changes and alopecia are not a diagnostic feature of chronic GvHD—that is, they may occur in the setting of chronic GvHD, but other histologic or laboratory criteria in the skin or other organs are required to render a diagnosis of chronic GvHD.[22]

The onset of chronic GvHD was classified as quiescent, de novo, or progressive according to history of prior acute GvHD. *Quiescent* onset was defined as the occurrence of chronic GvHD after complete resolution of acute GvHD; *de novo* onset indicated the appearance of chronic GvHD with no prior acute GvHD; and *progressive* onset indicated the onset of chronic GvHD without resolution of existing acute GvHD. The NIH Global Severity Score reflects the number of organs or sites affected with chronic GvHD, the disease severity at each affected organ, and the clinical effects of this involvement on the patient's functional status.[22] The NIH scores were categorized as *mild* (1–2 organs with a score of 1), *moderate* (≥3 organs with a score 1, any organ with a score of 2, or a lung with a score of 1), and *severe* (any organ with a score of 3 or a lung with a score ≥2).

Statistical Analysis

Univariate analysis was initially performed to screen for associations between factors of interest and development of vitiligo and/or AA. Relevant patient demographics, transplant history, chronic GvHD characteristics, and laboratory data were analyzed. Eleven autoantibodies were examined: antinuclear antibody, rheumatoid factor, anticyclic citrullinated peptides, antiparietal, anticentromere, antiribonucleoprotein, anti-smith, anticardiolipin (ACA) IgM, ACA-IgG, antiex-tractable nuclear antigens, and anti-thyroid

peroxidase auto-antibodies. Comparisons were made between patients with vitiligo and/or AA and patients without vitiligo and/or AA using the Wilcoxon rank sum test for continuous variables. The Cochran-Armitage test was used for ordered categorical variables,[24] and the Mehta modification of the Fisher exact test was used for unordered categorical variables.[25] Dichotomous variables were compared between the 2 groups using the Fisher exact test. Following an initial screening by univariate methods, multivariable logistic regression analysis was used to identify factors associated with the development of vitiligo and/or AA.

In view of the number of univariate tests performed, a 2-tailed *P* value such that $P < .005$ was considered statistically significant. All *P* values reported are 2 tailed and presented without any formal adjustment for multiple comparisons.

Results

Patient Demographic and Clinical Characteristics and Laboratory Parameters

Fifteen (5.3%) of 282 participants with vitiligo (14 of 282; 4.9%) and/or AA (2 of 282; 0.7%) were identified among 282 patients with chronic GvHD (Table 1). One patient had both vitiligo and AA. The median age of affected participants at enrollment was 38 years (age range, 9–69 years), and there was a male preponderance (10 of 15; 66.7%). Three patients (20.0%) were younger than 18 years. The most common indications for transplantation were chronic myelogenous leukemia (CML) (5 of 15; 33.3%) and acute leukemia or myelodysplastic syndrome (5 of 15; 33.3%). Most patients (13 of 15; 86.7%) had an HLA-identical donor and received peripheral blood stem cell transplantation (9 of 15; 60.0%). Eleven patients (73.3%) manifested concomitant skin chronic GvHD at the time of evaluation, most often sclerotic-type chronic GvHD (9 of 15; 60.0%). In 5 patients with documented onset of skin depigmentation, pigmentary changes developed a median of 41 months (range, 24–84 months) after transplant. Depigmentation was classic periorbital, perioral, acrofacial involvement in 6 patients (Figure 2A), generalized in 6 patients, and torso predominant in 2 patients. Trichrome vitiligo was present in 3 patients (Figure 2B), and poliosis occurred in 5 patients. Skin biopsies from depigmented skin were performed in 3 patients, revealing an absence of melanocytes in the basal layer confirmed by Melan-A immunohistochemical analysis. Hair loss was localized to the scalp in both patients with AA (Figure 2C).

Patient demographics, chronic GvHD characteristics, and laboratory parameters of patients with and without vitiligo and/or AA are listed in Table 2. In univariate analysis, female donor to male recipient (FtoM) sex mismatch ($P = .003$), positive ACA-IgG findings ($P = .03$), positive antiparietal antibody findings ($P = .049$), elevated CD19 level ($P = .045$), and normal or elevated IgG level ($P = .02$) were associated with vitiligo and/or AA. All 14 of 15 patients with vitiligo and/or AA with known donor sex had a female donor ($P < .001$). One patient with vitiligo was missing donor sex information. Of 3 donors with available parity data, 2 were previously pregnant.

Most patients with vitiligo and/or AA had been diagnosed as having chronic GvHD for more than 1 year (12 of 15; 80.0%) and had progressive-onset disease (9 of 15; 60.0%). As summarized in Table 2, autoantibodies were detected in 9 patients (60.0%; $P = .43$ vs those

without vitiligo and/or AA). The autoantibodies detected most frequently were antinuclear antibodies (5 of 14, 35.71%; $P = .78$), rheumatoid factor (4 of 15, 26.67%; $P = .11$), and ACA-IgG (4 of 15, 26.67%; $P = .03$). There were no significant differences in sex, indication for transplantation, conditioning regimen, chronic GvHD onset (quiescent, de novo, or progressive), chronic GvHD duration, or intensity of immunosuppression when patients with vitiligo and/or AA were compared with those without. Stem cell source (bone marrow, peripheral blood, or cord), donor and/or patient relationship (related or unrelated), HLA mismatch, receipt of donor lymphocyte infusion(s), type of skin chronic GvHD (sclerotic or nonsclerotic) and NIH Global Severity Score were also not associated with vitiligo and/or AA.

Multivariable Predictive Model of Vitiligoand/or AA Development

Number of CD19 cells, prevalence of antiparietal and ACA-IgG antibodies, and FtoM sex mismatch were included in a multivariable predictive model using logistic regression with backward selection. Donor sex ($P < .001$) was excluded as a potential parameter for inclusion in this model as a result of its infinite hazard ratio. The final model after backward selection included FtoM sex mismatch ($P = .003$) and ACA-IgG ($P = .01$). This model, when applied to the same patients on which the model was derived, correctly predicted 78.6% of patients with vitiligo and/or AA and 70.6% of those without vitiligo and/or AA.

Discussion

Allogeneic HSCT is a potentially curative treatment for refractory nonmalignant and malignant hematologic diseases; how-ever, its use is limited by the morbidity and mortality of acute and chronic GvHD. The pathogenesis of chronic GvHD involves dysregulation of both alloimmune and autoimmune mechanisms, resulting in autoantibody production, profibrotic pathways, and defective thymic function.[26,27]

Patients with vitiligo are at risk of AA and vice versa, and may also share common immunologic pathomechanisms. The prevalence of vitiligo and AA in the general population is 0.5% to 1.0% and 0.1%, respectively. Coexistence of vitiligo in patients with AA has been reported to be 3% to 8%.[28] Adaptive immunity, particularly infiltrative cytotoxic $CD8^+$ and $CD4^+$ T cells, very likely plays a key role in the destruction of melanocytes in vitiligo and hair loss in AA.[29–31]

Vitiligo and/or AA following allogeneic HSCT has been described in 15 case reports and/or series in the literature, 81% of which reported concurrent or prior skin GvHD (Table 3). In our cohort, CML and acute leukemia (acute lymphoblastic leukemia and/or acute myelogenous leukemia and/or myelodysplastic syndrome) were the most common disease indications for transplant. In previous reports, 38% of patients with chronic GvHD and vitiligo and/or AA underwent HSCT for CML, a frequency comparable with our findings. Notably, CML accounts for only about 300 of 7892 (3.8%) allogeneic HSCTs per year in the United States, a relative minority among indicated diseases.[32]

Allogeneic HSCT-associated vitiligo has been reported as localized disease (eg, face, trunk, limbs), generalized involvement, and total leukoderma. Our cohort manifested a variety of

vitiligo presentations, most frequently generalized and classic periorbital, perioral, and acrofacial distributions (Table 1). Trichrome vitiligo was observed in 3 patients. Total leukoderma, reported in 4 prior cases, was not seen in our cohort.

In contrast to prior cases, a large percentage (60.0%) of our cohort had sclerotic chronic GvHD, likely owing to the refractory nature of this skin manifestation and the referral pattern to the NIH. Sclerotic chronic GvHD manifests as a spectrum of clinical presentations, including localized fibrotic plaques resembling morphea with concomitant pigmentary changes as well as fibrosis limited to the papillary dermis resulting in white, shiny, guttate papules and plaques resembling LS.[4] It may be clinically challenging, then, to differentiate cutaneous chronic GvHD pigmentary abnormalities from true depigmentation suggestive of vitiligo. Interestingly, LS and vitiligo have been associated in the nonallogeneic HSCT setting (vitiligoid LS).[33] Lichenoid inflammation associated with LS triggering an autoimmune reaction against melanocytes has been proposed as a pathogenic mechanism.[34]

To our knowledge, this is the first study to describe an association between donor-recipient sex mismatch and the development of concomitant autoimmunity in patients with chronic GvHD. It is notable that in our cohort, all 14 patients with vitiligo and/or AA who had information on donor sex received their graft from a female donor. Nine of the 14 recipients were male, resulting in FtoM sex mismatch in 64.0% cases. Of 13 participants with chronic GvHD and vitiligo and/or AA in the literature with donor sex information, 8 (62%) had female donors and all were FtoM sex mismatch (Table 3).

Use of parous female donor and donor-recipient sex mismatch are important transplant risk factors for both acute and chronic GvHD.[35–38] Use of FtoM results in a higher probability of acute and chronic GvHD as well as poorer outcomes.[35–37,39–41] Interestingly, Kamoi et al[42] found a significant association between severe dry eye in patients with chronic GvHD and FtoM sex mismatch marrow transplant.

The risk of autoimmunity in FtoM transplants may reflect the activity of skin-homing donor T cells specific for recipient minor histocompatibility antigens encoded by Y-chromosome genes,[39] a mechanism previously implicated in both GvHD and graft-vs-tumor responses. In addition, prior studies indicate that presence of donor B-cell antibodies against the H-Y minor histocompatibility antigens may also contribute to the pathogenesis of chronic GvHD.[42,43] Tan et al[16] proposed that T-cell recognition of foreign melanocyte antigens may elicit a persistent immune response against host melanocytes. Likewise, a hallmark of active AA is the presence of $CD8^+$ T cells around the bulb region of anagen hair follicles.[44] Nonetheless, it is possible that the high percentage of FtoM sex mismatch reflects an epiphenomenon related to the high proportion of patients in our cohort with late-stage or treatment-refractory chronic GvHD.

Several additional theories have been proposed for depigmentation after allogeneic HSCT, including donor-transferred vitiligo,[6,45–48] chemoradiation therapy and/or donor lymphocyte infusion (DLI)–induced vitiligo,[6,11,13] and GvHD-associated vitiligo.[6,8,9,13,16,18] Adoptive transfer alloimmune destruction of melanocytes from donors with vitiligo has been

described in several reports.[6,45–48] No information regarding history of vitiligo from graft donors was available in our patients. A role of DLI has been hypothesized,[6] but we did not find a significant association between receipt of DLI(s) and vitiligo and/or AA. Interestingly, T cell–mediated vitiligo has been described in a patient who developed melanocyte destruction after antigen-specific immunotherapy form melanoma.[49] By the same token, the pretransplant conditioning regimen may render melanocytes susceptible to immune-mediated destruction through melanocyte-specific T cells or antimelanocyte antibodies triggered by chronic GvHD and/or thymic damage.[8,9,13] Sanli et al[18] suggested tumor necrosis factor (TNF) as a possible mediator of vitiligo. Elevations of TNF and interleukin 6 have been found in vitiligo skin[50] and observed in the induction of chronic GvHD.[51] Four patients in our cohort did not manifest concomitant chronic GvHD skin involvement, supporting the theory that vitiligo and/or AA can be triggered or persist without localized chronic GvHD skin involvement. Genetic risk factors of both the host and donor, specifically HLA predispositions to vitiligo, may also play a role in disease pathogenesis. In 3 patients with vitiligo in whom HLA recipient data was available, each had 1 or more HLA alleles (*DRB1*04*, *−07*, *−07:01*) that have been associated with vitiligo in specific Asian and European populations.[52,53] Interestingly, these 3 individuals also demonstrated HLA alleles (*DRB1*07:01*, *DQB1*02:02*, *DQB1*06:02*) that have been associated with alopecia areata.[54]

Outside the setting of HSCT, vitiligo and AA are frequently associated with autoantibody formation. Autoantibodies, particularly low-titer antinuclear antibody, are commonly detected in chronic GvHD[55]; however, their clinical significance is unclear because they lack the specificity seen in other well-characterized autoimmune conditions and are not associated with disease severity. In our cohort, the only antibody significantly associated with vitiligo and/or AA development was ACA-IgG. Antiphospholipid antibodies recognize phospholipid protein complexes and include lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein I antibodies. Anticardiolipins have been detected in patients with systemic lupus erythematosus, systemic sclerosis, scleroderma, and Sjögren syndrome.[56–58] Our study suggests that ACA-IgG in patients with chronic GvHD may be a risk factor for cutaneous autoimmunity.

Vitiligo and AA are associated with other autoimmune disorders, including thyroid disease, diabetes mellitus, and pernicious anemia.[59] In our chronic GvHD cohort, patients 8 and 9 had a diagnosis of Hashimoto thyroiditis prior to transplantation, and patient 8 had associated anti-thyroid peroxidase antibodies. Patients 2, 4, and 10 were found to have elevated levels of thyroid stimulating hormone with no documented evidence of thyroid disorders prior to transplantation. Thus, it is reasonable to screen for thyroid function abnormalities and other autoimmune diseases in patients with chronic GvHD vitiligo and/or AA.

There are several limitations of this study. First, the cross-sectional design restricts our evaluation to chronic GvHD manifestations and, specifically, cutaneous features at a single point in time. Similarly, laboratory data, including all blood analyses, may not be reflective of earlier points in each patient’s disease course. Furthermore, the cross-sectional design does not establish causality of the relationship between donor-recipient sex combinations

and development of vitiligo. In addition, date of vitiligo onset was determined from review of patient records and was only available in a minority of patients in our subset. The NIH chronic GvHD natural history protocol referral pattern is also highly enriched for longstanding, treatment-refractory chronic GvHD and therefore is not reflective of all patients with chronic GvHD, particularly those with less severe disease. Nonetheless, the cross-sectional study design provides a powerful method to detect rare skin manifestations in a large patient cohort.

Conclusions

Vitiligo and/or AA are uncommon phenomena seen in allogeneic HSCT recipients and are likely secondary to the long-term immune dysregulation of chronic GvHD. In our cohort, ACA and female donor sex, in particular FtoM sex mismatch, were associated with risk of vitiligo and/or AA. Although vitiligo and AA are not life threatening, the psychological consequences in patients with chronic GvHD can further impair quality of life. Future studies are needed to clarify whether the risk factors identified in this study could lead to better understanding of other autoimmune manifestations in the setting of chronic GvHD.

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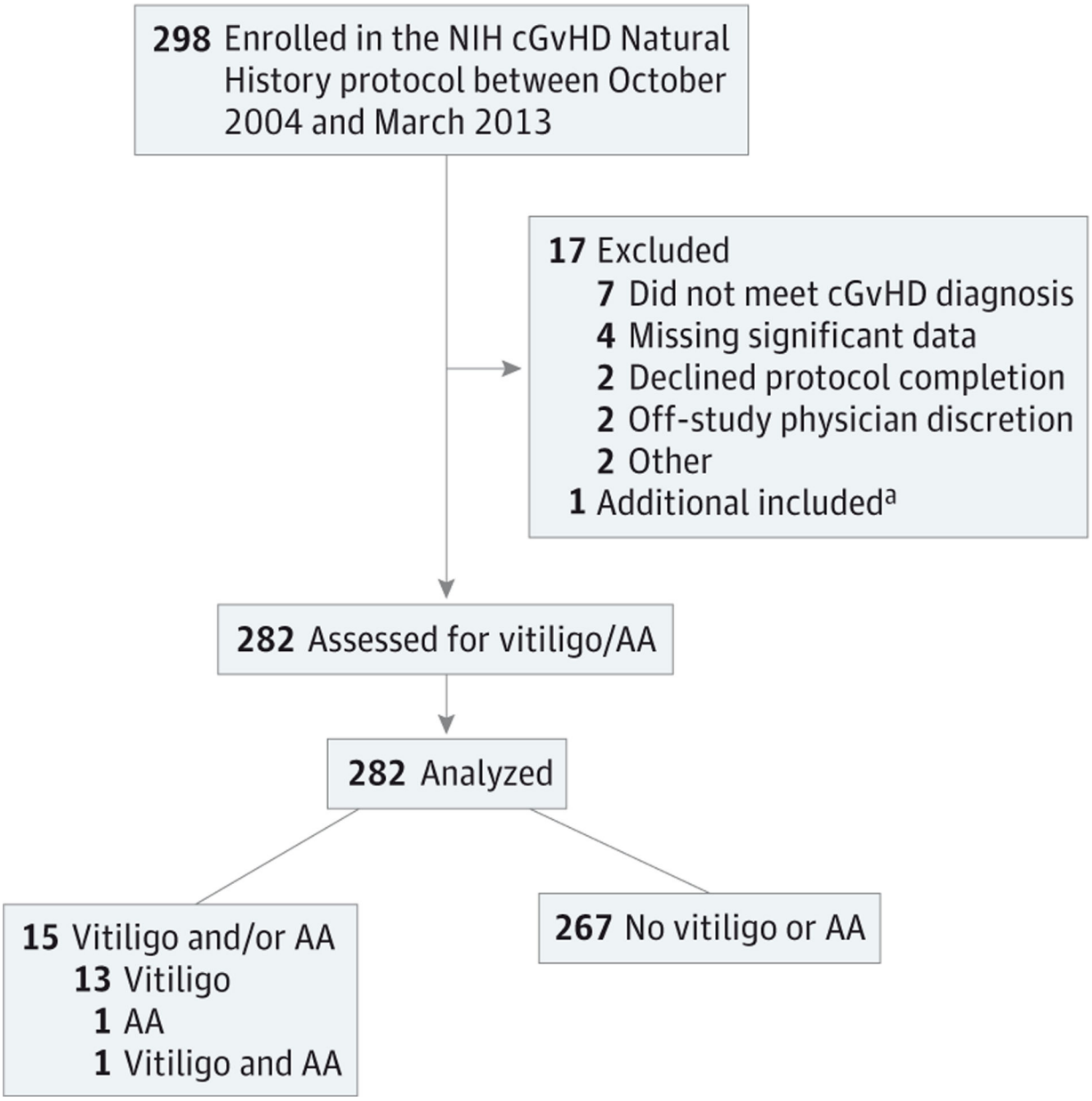

Figure 1.

Flow Diagram for Patient Enrollment and Progress Through the Study

AA indicates alopecia areata; cGvHD, chronic graft-vs-host disease; NIH, National Institutes of Health.

[a]One additional patient (with vitiligo) was identified for inclusion in this study just prior to statistical analysis.

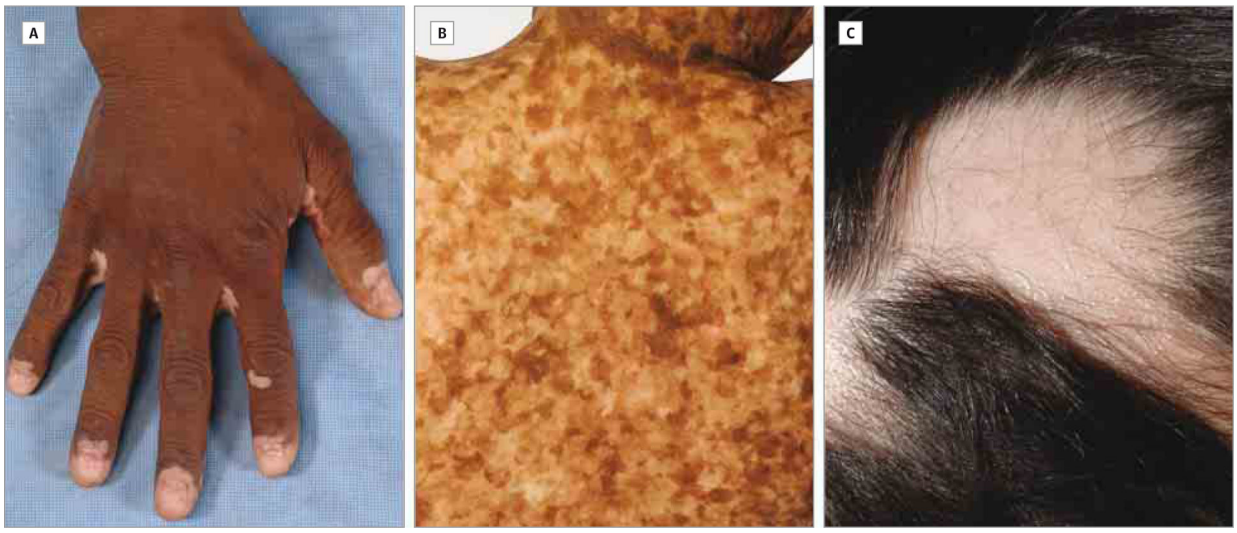

Figure 2.

Clinical Spectrum of Vitiligo and Alopecia Areata in the Setting of Chronic Graft-vs-Host Disease

A, Depigmentation involving the distal ends of the fingers in this clinical image of classic vitiligo. B, An intermediate zone of hypopigmentation is present between depigmented and normal skin in trichrome vitiligo. C, Patchy oval areas of hair loss on the scalp characterize classic-appearing alopecia areata.

Table 1.

Characteristics of Patients With cGvHD and Vitiligo and/or AA

					Vitiligo and/or AA			cGvHD Involvement
Patient No./ Sex[a,b,c]	**Disease**	**Transplant Conditioning**	**Graft Type**	**Time to Occurrence, mo**	**Distribution**	**Vitiligo Type**	**Skin**	**Other Organs**
1/M	CML	Bu/Cyc	BM	24	Perioral, torso, R buttock, pretibial legs	Torso	Epid	Eyes, lungs, liver
2/M	APL	…	PB	…	Periorbital/oral, head/neck, back, fingers	Classic[d]	Both[e]	Eyes, oral, GI
3/F	FNHL	Flu/Cyc	PB	…	Periorbital, perioral, L cheek, back	Classic[d]	Epid	Eyes
4/M	RMSA	Flu/Cyc/Mel	PB	…	B/L cheeks, head/neck, upper chest, UE, LE	Generalized	Both[e]	Eyes, oral, lungs, joint
5/M	CML	Bu/Cyc/VP-16	BM	…	Perioral	Classic[d]	Both[e]	Eyes, oral, GI, joint
6/M	CML	Bu/Flu/ATG	BM	36	Perioral, cheeks, acral, UE, genitalia	Classic[d]	Both[e]	Eyes, oral, GI, liver, genital
7/F	CML	Bu/Flu/ATG	PB	…	Trichrome face, chest, upper back, B/L thighs	Classic[d]	None	Eyes, oral, lungs, GI, joint
8/M[a,b]	WAS	…	Cord	…	Diffuse trichrome vitiligo	Generalized	Both[e]	Lungs, joint
9/F	AML	Flu/TBI	PB	36	Face, chest, lower back, B/LUE, LE	Generalized	Scl	Eyes, oral, lungs, GI, joint
10/F[b,c]	AML	Flu/Cyc/TBI	Cord	…	Vitiligo: face, postauricular, neck, trunk, UE, LE AA: scalp vertex	Generalized	Epid	Lungs, vulvovaginal
11/M	CLL	Flu/Cyc	PB	…	Face, scalp, neck, anterior trunk	Generalized	Both[e]	Eyes, oral, liver, joint
12/M	B-cell ALL	Cyc/TBI	PB	…	Periorbital, perioral, scalp, chin	Classic[d]	Epid	Oral, lungs
13/F	CTCL	Flu/Mel	PB	…	Neck, trunk, proximal UE	Torso	Both[e]	Eyes, lungs, GI, liver, genital
14/M	CML	Bu/Cyc	PB	84	Trichrome face, trunk, B/LUE	Generalized	Both[e]	Eyes, oral, lungs, liver
15/M[c]	ALL	Cyc/VP-16/TBI	BM	24	Scalp	NA	None	Lungs, GI

Abbreviations: AA, alopecia areata; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; APL, acute promyelocytic leukemia; ATG, antithymocyte globulin; B/L, bilateral; BM, bone marrow; Bu, busulfan; cGvHD, chronic graft-vs-host disease; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CTCL, cutaneous T-cell lymphoma; Cyc, cyclophosphamide; epid, epidermal; Flu, fludarabine; FNHL, follicular non-Hodgkin lymphoma; GI, gastrointestinal tract; L, left; LE, lower extremities; Mel; melphalan; NA, not applicable; PB, peripheral blood; R, right; RMSA, rhabdomyosarcoma; Scl, sclerotic; TBI, total body irradiation; UE, upper extremities; VP-16, etoposide; WAS, Wiskott-Aldrich syndrome; …, not known.

[a]All patients whose donor sex was known received transplants from female donors; donor sex for patient 8 was not reported.

[b]Thirteen of the 15 patients had an HLA-identical donor; a mismatch occurred only with patients 8 and 10.

[c] Thirteen of the 15 patients had only vitiligo; patient 10 had both vitiligo and AA; patient 15 had only AA.

[d] Classic indicates predominantly perioral, periorbital, and acrofacial involvement; torso, predominantly truncal involvement; generalized, diffuse involvement.

[e] Both indicates both sclerotic and epidermal cGvHD involvement.

Table 2.

Clinical Characteristics and Laboratory Data of Patients With cGvHD With and Without Vitiligo and/or Alopecia Areata[a]

Characteristic	Total (n = 282)	No Vitiligo or AA (n = 267)	Vitiligo and/or AA (n = 15)	*P* Value
Age, median (range), y	46 (4–70)	46 (4–70)	38 (9–69)	.30
≤18 y	20/282 (7.09)	17/267 (6.37)	3/15 (20.00)	…
Sex				
Male	160/282 (56.73)	150/267 (56.18)	10/15 (66.67)	.59
Female	122/282 (43.26)	117/267 (43.82)	5/15 (33.33)	
Primary disease				
ALL/AML/MDS	128/282 (45.39)	123/267 (46.07)	5/15 (33.33)	.22
CML	39/282 (13.82)	34/267 (12.73)	5/15 (33.33)	
CLL	17/282 (6.03)	16/267 (5.99)	1/15 (6.67)	
Malignant lymphoma	64/282 (22.69)	62/267 (23.22)	2/15 (13.33)	
Other[b]	34/282 (12.06)	32/267 (11.99)	215 (13.33)	
Conditioning regimen				
TBI−/MAC−	100/279 (35.84)	94/265 (35.47)	6/14 (42.86)	.93
TBI+/MAC−	24/279 (8.60)	23/265 (8.68)	1/14 (7.14)	
TBI−/MAC+	74/279 (26.52)	70/265 (26.42)	4/14 (28.57)	
TBI+/MAC+	81/279 (29.03)	78/265 (29.43)	3/14 (21.43)	
MAC	155/279 (55.56)	148/265 (55.85)	7/14 (50.00)	.78
RIC	124/279 (44.44)	117/265 (44.15)	7/14 (50.00)	…
TBI	105/279 (37.63)	101/265 (38.11)	4/14 (28.57)	.58
DLI post transplant				
Yes	25/262 (9.54)	24/247 (9.72)	1/15 (6.67)	>.99
No	247/262 (94.27)	223/247 (9.28)	14/15 (93.33)	
Stem cell source				.05
BM	53/282 (18.79)	49/267 (18.35)	4/15 (26.67)	.49
PB	219/282 (77.66)	210/267 (78.65)	9/15 (60.00)	.11
Cord	10/282 (3.55)	8/267 (3.00)	2/15 (13.33)	.09

Characteristic	Total (n = 282)	No Vitiligo or AA (n = 267)	Vitiligo and/or AA (n = 15)	*P* Value
Donor relationship				
Related	174/281 (61.92)	163/266 (61.28)	11/15 (73.33)	.42
Unrelated	107/281 (38.08)	103/266 (38.72)	4/15 (26.67)	
HLA matched				
Yes	230/275 (83.64)	217/260 (83.46)	13/15 (86.67)	>.99
No	45/275 (16.36)	43/260 (16.54)	2/15 (13.33)	
Donor sex				
Male	135/255 (52.94)	135/241 (56.02)	0/14	<.001
Female	120/255 (47.06)	106/241 (43.98)	14/14 (100)	
Donor to patient sex match or mismatch				<.001
M to M	76/256 (30.08)	76/242 (31.82)	0/14	…
F to F	57/256 (21.88)	52/242 (21.07)	5/14 (35.71)	…
M to F	55/256 (21.88)	55/242 (22.73)	0/14	.05
F to M	68/256 (26.17)	59/242 (24.38)	9/14 (64.29)	.003
cGvHD duration, y				
≤1	79/282 (28.01)	76/267 (28.46)	3/15 (20.00)	.57
≥1	203/282 (71.99)	191/267 (71.54)	12/15 (80.00)	
cGvHD onset				
Quiescent	77/280 (27.50)	75/265 (28.30)	2/15 (13.33)	.31
De novo	92/280 (32.86)	88/265 (33.21)	4/15 (26.67)	
Progressive	111/280 (39.64)	102/265 (38.49)	9/15 (60.00)	
Intensity of immunosuppression[c]				
None or mild	70/281 (24.91)	66/266 (24.81)	4/15 (26.67)	>.99
Moderate	100/281 (35.59)	95/266 (35.71)	5/15 (33.33)	
High	111/281 (39.5)	105/266 (39.47)	6/15 (40.00)	
Presence of skin cGvHD[d]				
Yes	215/281 (76.51)	202 (75.70)	13/15 (86.67)	.53
No	66/281 (23.49)	64/266 (24.06)	2/15 (13.33)	
Median BSA, %				

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Characteristic	Total (n = 282)	No Vitiligo or AA (n = 267)	Vitiligo and/or AA (n = 15)	*P* Value
Erythema	0.81	0.86	0.54	.96
Sclerosis	0	2.16	0.36	.81
NIH Global Severity score				
Moderate	81/278 (29.14)	74/264 (71.97)	7/14 (50.00)	.13
Severe	197/278 (70.86)	190/264 (71.97)	7/14 (50.00)	
Laboratory parameters				
Presence of autoantibodies	133/279 (47.67)	124/264 (46.97)	9/15 (60.00)	.43
ANA	90/278 (32.37)	85/264 (32.20)	5/14 (35.71)	.78
RF	35/275 (12.73)	31/260 (11.92)	4/15 (26.67)	.11
Anti-CCP	20/277 (7.22)	18/262 (6.87)	2/15 (13.33)	.30
Antiparietal	7/277 (2.53)	5/262 (1.91)	2/15 (13.33)	.05
Anticentromere	9/277 (3.25)	8/262 (3.05)	1/15 (6.67)	.40
Anti-RNP	14/279 (5.02)	12/264 (4.55)	2/15 (13.33)	.17
Anti-smith	3/279 (1.08)	2/264 (0.76)	1/15 (6.67)	.15
ACAIgM	22/277 (7.94)	21/262 (8.02)	1/15 (6.67)	>.99
ACAIgG	23/277 (8.30)	19/262 (7.25)	4/15 (26.67)	.03
Anti-ENA	23/279 (8.24)	21/264 (7.95)	2/15 (13.33)	.36
Anti-TPO	3/59 (5.08)	2/51 (3.92)	1/8 (12.50)	.36
Low CD3 (<1000/UL)	156/261 (59.77)	149/247 (60.32)	7/14 (50.00)	.58
Low CD4 (<250/UL)	80/263 (30.42)	77/249 (30.92)	3/14 (21.43)	.56
Low CD19 (<400/UL)	199/282 (70.57)	192/267 (71.91)	7/15 (46.67)	.05
High IgG (>1200 mg/dL)	46/278 (16.55)	41/263 (15.59)	5/15 (33.33)	.02[e]

Abbreviations: AA, alopecia areata; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; ANA, antinuclear antibody; BM, bone marrow; BSA, body surface area; CCP, cyclic citrullinated peptides; cGvHD, chronic graft-vs-host disease; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DLI, donor lymphocyte infusion; ENA, extractable nuclear antigens; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; NIH, National Institutes of Health; PB, peripheral blood; RIC, reduced-intensity conditioning; RF, rheumatoid factor; RNP, ribonucleoprotein; TBI, total body irradiation; TPO, thyroid peroxidase; …, analysis not performed.

[a] Unless otherwise indicated, data are reported as number of participants/total number in the category (percentage).

[b] The “other” category includes patients with multiple myeloma, sarcoma, immunodeficiency, aplastic anemia and/or paroxysmal nocturnal hemoglobinuria, and nonmalignant diseases.

[c] *Mild immunosuppression* defined as single-agent prednisone at less than 0.5 mg/kg/d; *moderate*, prednisone at 0.5 mg/kg/d or higher and/or any other single agent or modality; *high*, 2 or more agents or modalities with or without prednisone at 0.5 mg/kg/d.

[d] Indicates both sclerotic and/or nonsclerotic dermatologic manifestations of cGvHD.

[e] *P* value relates to the comparison across low vs normal vs high IgG.

Table 3.

Reported Cases of Non–Donor Transferred Vitiligo and/or AA Occurring After Allogeneic HSCT

					Vitiligo and/or AA			
Source, Year	**Patient Sex/ Age, y**	**Donor Sex**	**Disease**	**Transplant Conditioning**	**Condition**	**Time to Occurrence[a]**	**Distribution**	**Type of Skin GvHD**
Nagler et al,[13] 1996	M/14	NR	SAA	TLI/Cyc	Vitiligo	3 mo	Total leukoderma, leukotrichia	cGvHD-Lich
Aubin et al,[7] 2000	M/44	F	CML	Cyc/Thiotepa/TBI	Vitiligo	5 mo	Generalized	cGvHD-Lich
Au et al,[6] 2001	M/35	NR	CML	NR	Vitiligo	3 y	Generalized, leukotrichia	aGvHD grade 4
	F/36	NR	ALL	NR	Vitiligo	3–5 y	Generalized	aGvHD grade 3
Jacobsohn et al,[11] 2002	M/14	NR	CML	Bu/Ara-C/TBI	Vitiligo	5 mo	Total leukoderma, leukotrichia	cGvHD-Lich
Sanli et al,[19] 2004	M/26	NR	AML	Bu/Cyc	AA	6 mo	Left parietal, vertex, lateral right eyebrow	cGvHD-Lich
	M/19[b]	NR	CML	Bu/Cyc	Vitiligo and AA	8 mo	Vitiligo: face, neck, trunk, UE/LE; AA: temporal/ occipital	NR
	M/31	NR	CML	Bu/Cyc	AA	3 mo	Eyebrows, forearms	NR
Cho et al,[9] 2005	M/15	NR	ALL	Cyc/TBI	Vitiligo	3 mo	Generalized	aGvHD
	M/30	F	CML	Cyc/TBI	Vitiligo	2 y	Generalized	aGvHD
	M/28	F	ALL	Cyc/TBI	Vitiligo	26 mo	Generalized	cGvHD-Scl
	M/43	F	MDS	Bu/TBI/Cyc	Vitiligo	3 mo	Face, UE	cGvHD
Williams et al,[17] 2008	M/55	NR	MDS	NR	Vitiligo	3 y	Total leukoderma, leukotrichia	cGvHD-Epid
	M/66	NR	MDS	RIC	Vitiligo	3 y	Generalized	cGvHD
Cathcart and Marrell,[8] 2007	M/15	M	FA/AML	Flu/TBI/Cyc/AT G	Vitiligo	4 y	Hands, arms, neck, trunk, genitalia	aGvHD
Sanli etal,[18] 2008	M/34	M	CML	Bu/Cyc	Vitiligo	4 y	Generalized, leukotrichia	cGvHD-Lich
	M/19[b]	M	CML	Bu/Cyc	Vitiligo and AA	8 mo	AA: temporal, occipital; Vitiligo: face, neck, trunk, UE/LE	NR
	M/44	F	CML	Bu/Cyc	Vitiligo	7 mo	Face, hair, eyelids, trunk, UE/LE	cGvHD-Fol
	M/44	F	CML	Bu/Cyc	Vitiligo	4 y[c]	Face, dorsum of hands	cGvHD-Scl
	F/41	M	CML	Bu/Flu	Vitiligo	6 mo	Face	NR
Heath et al,[10] 2009	F/2	NR	SCID	Bu/Cyc/ATG	Vitiligo	4 mo	Chest, arms, legs, face, scalp	aGvHD

					Vitiligo and/or AA			
Source, Year	**Patient Sex/ Age, y**	**Donor Sex**	**Disease**	**Transplant Conditioning**	**Condition**	**Time to Occurrence[a]**	**Distribution**	**Type of Skin GvHD**
	M/5	NR	X-SCID	Bu/Cyc	Vitiligo	NR	Diffuse depigmentation, scattered leukotrichia	aGvHD
Lee etal,[12] 2009	M/23	F	SAA	Cyc	Vitiligo	2 y	Face, trunk, UE/LE	NR
Tan et al,[16] 2011	F/48	M	MDS	Cyc/Bu	Vitiligo	5 y[d]	Face, trunk, UE/LE	cGvHD-Lich, Scl
Kamińska et al,[20] 2012	M/38	NR	aApAn	Flu/Alemtuzumab/Mel	AA	6 mo	Diffuse alopecia	cGvHD
Oh and Lee,[15] 2013	F/36	NR	ALCL	NR	Vitiligo	3 wk	UE/LE, trunks	NR
Nambudiri et al,[14] 2013	M/15	F	X-SCID	None	Vitiligo	1 mo	Total leukoderma, leukotrichia	cGvHD-Scl

Abbreviations: AA, alopecia areata; aApAn, acquired aplastic anemia; aGvHD, acute graft-vs-host disease; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; Ara-C, cytarabine; ATG, antithymocyte globulin; Bu, busulfan; cGvHD, chronic graft-vs-host disease; CML, chronic myelogenous leukemia; Cyc, cyclophosphamide; Epid, epidermal; FA, Fanconi anemia; Flu, fludarabine; HSCT, hematopoietic stem cell transplantation; LE, lower extremities; Lich, lichenoid; MDS, myelodysplastic syndrome; Mel, melphalan; NR, not reported; RIC, reduced-intensity conditioning; SAA, severe aplastic anemia; SCID, severe combined immunodeficiency; Scl, sclerotic; TBI, total body irradiation; TLI, total lymph node irradiation; UE, upper extremities; X-SCID, x-linked SCID.

[a] Indicates time from allogeneic HSCT to onset of vitiligo or AA.

[b] The case by Sanli et al 2008 may represent the same patient as the 19-year-old patient in Sanli et al 2004.

[c] The donor (sister) of this patient had generalized vitiligo for 10 y. The authors postulate that the development of vitiligo 4 years after transplant was not likely from passive donor transfer.

[d] This patient received 2 allogeneic HSCTs; the time shown refers to time after the second allogeneic HSCT.