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Vitiligo-like manifestations of graft-versus-host disease in a pediatric population

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Abstract

Vitiligo-like changes are an uncommon cutaneous manifestation of graft-versus-host disease (GVHD). We report three cases and review the literature of pediatric patients with vitiligo-like changes associated with GVHD. Improved characterization of this phenomenon may lend insight into the biologic pathways that underlie both vitiligo and GVHD.

KEYWORDS
depigmentation, graft-versus-host disease, hypopigmentation, leukoderma, vitiligo

1 | INTRODUCTION

Graft-versus-host disease (GVHD) is a multiorgan disorder that is a major cause of morbidity and non-relapse mortality in patients after hematopoietic stem cell transplantation (HSCT). Cutaneous manifestations are characterized by clinical and histopathologic features that may resemble autoimmune disorders of the skin, such as scleroderma and lichen planus. These similarities are thought to be due to shared immunologic pathways and may explain the collective response to immunosuppressive therapies. Vitiligo-like lesions have been reported in 1.78% of patients after HSCT with a higher incidence of 8% in patients with GVHD of any site.[1–3] In a cohort of 85 pediatric patients post-HSCT, 12 (14%) reported having subsequent vitiligo, with 8 having a history of GVHD.[4] As vitiligo is an autoimmune T-cell mediated process, recapitulation of this phenomenon in patients with GVHD is thought to be attributable to similar pathophysiologic mechanisms. We present three patients and review the literature on vitiligo-like findings in pediatric patients with GVHD of any site.

2 | CASE REPORTS

2.1 | Patient 1

A 16-year-old female with sickle cell anemia underwent allogeneic bone marrow transplantation (BMT) from a matched, unrelated donor after conditioning with busulfan, cyclophosphamide, and antithymocyte globulin (ATG). She developed GVHD of the skin and liver, initially responsive to immunosuppressive therapies. Five months after HSCT, she developed depigmented macules and patches on the face, trunk, and extremities that accentuated upon Wood's lamp examination. There was no known personal or family history of pigmentary conditions. Skin lesions were refractory to topical steroids, topical calcineurin inhibitors, and narrowband ultraviolet radiation (nbUVB). Nineteen months after HSCT, she developed new scaly, hypo-, and hyperpigmented macules and thin papules on the face, trunk, and extremities. Skin biopsy demonstrated findings consistent with lichenoid GVHD. Over the subsequent months, her skin lesions became more sclerotic, and she developed GVHD of the oral and ocular mucosa, liver, and lungs that was refractory to treatment with extracorporeal photopheresis and pentostatin.

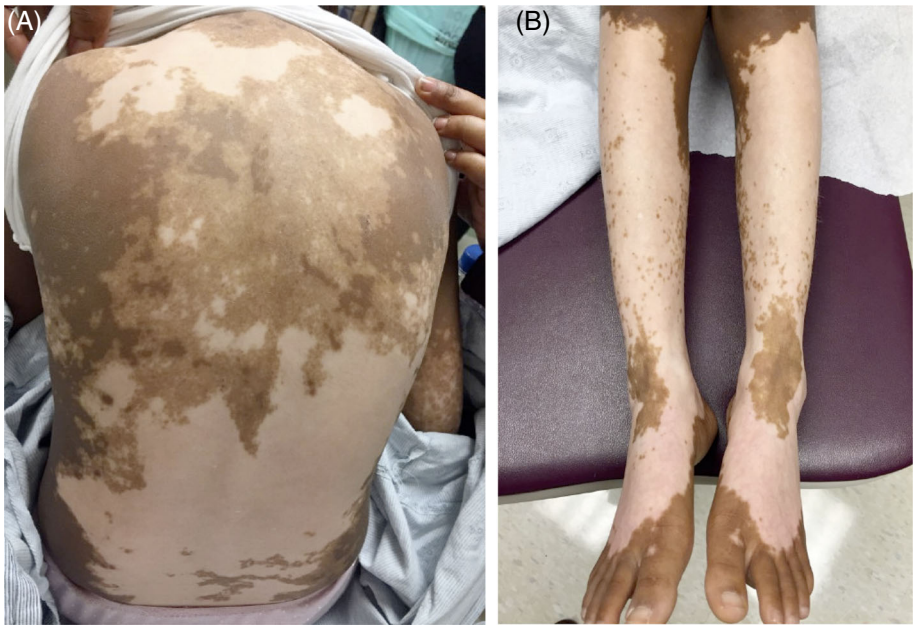

FIGURE 1 Extensive depigmented patches at sites of prior dermatitis on the legs (A) and trunk (B) of patient 2

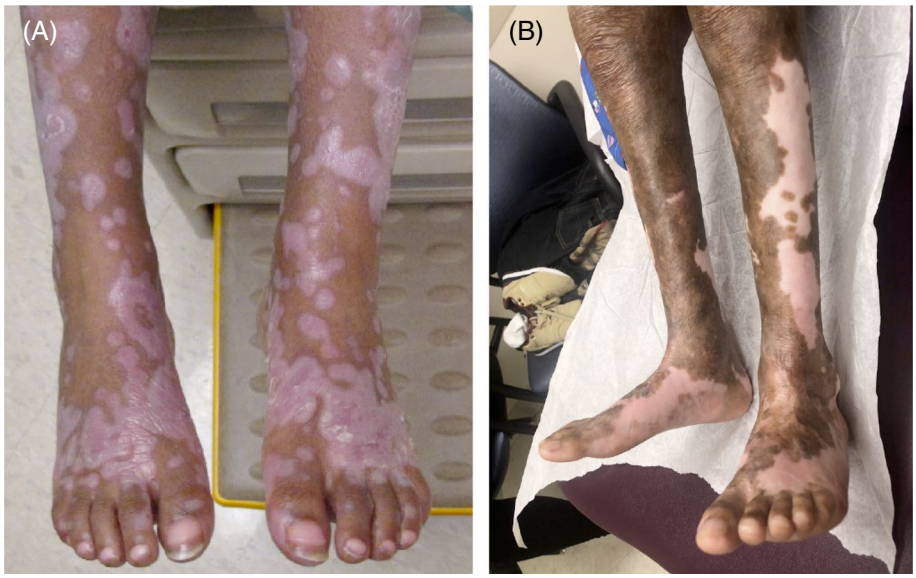

FIGURE 2 Violaceous plaques (A) that evolved into depigmented patches (B) on the lower extremities of patient 3

2.2 | Patient 2

A 12-year-old female with beta thalassemia major underwent allogeneic BMT from a haploidentical, related donor after conditioning with busulfan, fludarabine, cyclophosphamide, thiotepa, and ATG. Three months after HSCT, she developed a widespread papular eruption, and skin biopsy demonstrated findings compatible with lichenoid GVHD. She was later diagnosed with ocular and pulmonary GVHD and underwent treatment with photopheresis, systemic tacrolimus, and cyclosporine. Sixteen months after BMT, she developed depigmented patches and poliosis at sites of prior dermatitis comprising 75% body surface area (Figure 1). There was no known personal or family history of pigmentary conditions. Skin lesions were refractory to treatment with topical steroids.

2.3 | Patient 3

A 3-year-old male with chronic granulomatous disease underwent allogeneic BMT from a matched, unrelated donor after conditioning with busulfan, cyclophosphamide, and alemtuzumab. He underwent a bone marrow boost 4 months after HSCT due to decreasing chimerism. Five months after HSCT, he developed a widespread papular eruption that was biopsied and consistent with GVHD. He was diagnosed with gastrointestinal and liver GVHD and managed with photopheresis, sirolimus, pentostatin, and imatinib. In the 3 years following HSCT, his eruption evolved into violaceous, sclerodermoid plaques prior to developing into depigmented patches (Figure 2). Neither the patient, his family, nor his donor had a history of pigmentary conditions. Skin lesions were refractory to topical steroids, topical calcineurin inhibitors, and nbUVB.

TABLE 1 Characteristics of 16 pediatric patients

Sex/ Age	Disease/Tx type	HLA compatibility	Donor sex	Time to skin lesions	Distribution of skin lesions	Histopathologic findings	Skin-directed treatments	Treatment response	aGVHD	cGVHD
M/14Y[5]	Aplastic anemia/AlloBMT	Matched	—	4 m	Total leukoderma	—	None	—	Skin, GI, liver	Skin
M/14Y[6]	CML/AlloBMT	Matched	—	5 m	Total leukoderma	Vitiligo	None	—	None	Skin
M/15Y[7]	ALL/AlloBMT	Matched	—	3 m	Generalized	Vitiligo	nbUVB	PR	Skin, GI	None
M/15Y[8]	AML/Peripheral blood	Mismatched	M	4y	Generalized	—	TCS, TCI	SD	Skin, liver	None
M/11Y[9]	Sickle cell disease/AlloBMT	Matched	M	13 m	Generalized	—	—	—	Skin, GI	None
F/2M[10]	SCID/Cord blood	Matched	—	4 m	Generalized	Eczematous	TCI	PR	Skin, GI	None
M/1Y[10]	SCID/Cord blood	Mismatched	—	39 m	Total leukoderma	—	—	—	Skin	Skin
M/3Y[11]	ALL/AlloBMT	—	—	6 m	Generalized	Vitiligo	TCI	SD	Skin, liver, GI	None
M/3Y[12]	ALL/Peripheral blood	—	F	28 m	Localized	Vitiligo	TCS	SD	Not specified	Not specified
M/2Y[13]	LCH/Liver transplant	Mismatched	M	12 m	Generalized	—	None	—	Skin, GI	None
M/8M[14]	SCID/AlloBMT	Haploidentical	F	17d	Total leukoderma	Vitiligo	None	—	Skin	Skin, GI, liver, lungs
M/9Y[15]	AML/AlloBMT	—	—	12 m	Generalized	—	—	—	Skin, GI	Skin, GI
M/8Y[16]	ALL/AlloBMT	—	F	7 m	Generalized	GVHD	TCS, TCI	SD	None	Skin
F/16Y[†]	Sickle cell disease/AlloBMT	Matched	F	5 m	Generalized	GVHD	TCS, TCI, nbUVB	SD	Skin, liver	Skin, liver, lungs, ocular
F/12Y[†]	Beta thalassemia major/ AlloBMT	Haploidentical	M	16 m	Generalized	—	TCS	SD	Skin, lungs, ocular	Skin, ocular
M/3Y[†]	Chronic granulomatous disease/AlloBMT	Matched	—	3y	Generalized	—	TCS, TCI, nbUVB	SD	Skin, GI, liver	Skin

Abbreviations: AlloBMT, allogeneic bone marrow transplantation; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; d, day; F, female; GI, gastrointestinal; GVHD, graft-versus-host-disease; LCH, langerhans cell histiocytosis; m, months; M, male; nbUVB, narrowband ultraviolet B phototherapy; PR, partial response; SCID, severe combined immunodeficiency; SD, stable disease; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; y, years.

[†]cases described in the current report.

3 | DISCUSSION

Our literature search yielded 13 pediatric patients who developed vitiligo-like changes associated with GVHD (Table 1). Of the 16 total cases (including the three patients in this report), median age was 8 years (range, 2 months to 16 years). Thirteen (81%) patients were male, and the most common indication for transplantation was chronic and acute leukemia (7/16, 44%). Most patients underwent an allogeneic BMT (11/16, 69%) from an HLA-identical (7/12 evaluable patients, 58%) and related donor (8/16, 50%). One patient underwent liver transplantation and developed near full donor chimerism. Median time from transplantation to onset of vitiligo-like lesions was 9.5 months (range, 17 days to 48 months). Eleven patients (69%) developed multiple vitiligo-like lesions in a generalized distribution, and four patients (25%) were described to have total leukoderma with no areas of residual normal pigmentation. Seven cases (44%) noted associated poliosis. Fifteen of 16 cases reported cutaneous GVHD; one case did not specify the affected organ system. None of the patients reported a personal history of vitiligo. Eight cases reported histopathology with five cases (63%) demonstrating findings consistent with vitiligo and two cases (25%) showing features compatible with GVHD. Although nine patients reported treatment with topical steroids, topical calcineurin inhibitors, or nbUVB, only two cited clinical improvement.

Our case series and review characterize 16 pediatric patients who developed vitiligo-like changes associated with GVHD and illustrate the heterogeneous clinical and histological findings within this cohort. The majority of patients reviewed (81%) were male, which recapitulates findings of a previous review that reported a male predominance of 80.5%.[1] Other cohort studies of vitiligo-like changes describe a male prevalence of 62.0%–66.7%, though this may be at least partially attributable to the increased male: female ratio in patients undergoing HSCT.[16] Zuo et al. noted an association between female donor to male recipient (FtoM) sex mismatch and vitiligo-like changes following HSCT.[17] FtoM sex mismatch has been independently associated with GVHD and is thought to be mediated by female donor T-cells targeting male recipient minor histocompatibility antigens.[18] However, a cohort study of pediatric HSCT recipients found no significant association between vitiligo and donor/recipient sex discordance.[4] Three of 13 males in our cohort had female donors; however, data on donor sex was unavailable for 7 of 10 remaining male patients. Further study is needed into whether male sex and FtoM sex mismatch are independent risk factors for vitiligo-like changes.

Nearly all patients reviewed had co-existent cutaneous GVHD (the remaining case did not describe GVHD subtype). Although we included only patients with a history of GVHD of any site for review, the strong correlation of vitiligo-like changes with a history of cutaneous GVHD (rather than GVHD of other sites) supports the theory shared by many authors that pigmentary changes are secondary to a GVHD-triggered immune response selectively targeting melanocyte destruction.[5,7,19] Factors that contribute to an increased risk of GVHD, such as history of donor lymphocyte infusion, have also been associated with the development of vitiligo-like changes.[19] In many cases in our review, pigmentary changes progressed even after resolution of cutaneous GVHD, a finding that suggests that, although cutaneous GVHD may play a role in triggering these pigmentary changes, subsequent progression of vitiligo-like changes may occur independently and as a result of other risk factors, such as koebnerization.[20]

The incidence of generalized vitiligo and total leukoderma in our review is disproportionately high compared to previous studies of de novo vitiligo in pediatric patients, in which segmental type is seen in up to one-third of those affected.[21] This discrepant distribution of clinical subtypes suggests that the pathophysiology of vitiligo-like changes associated with HSCT is distinct and may be associated with a more widespread presentation. In two of three cases from our institution, localization of vitiligo-like lesions closely mirrored areas previously involved by GVHD, which is a phenomenon that has not been well-described in the literature and underscores the challenge in differentiating true depigmentary changes in vitiligo from hypopigmentation from prior dermatoses, including prior GVHD.

Although skin biopsies are frequently recommended to help characterize dermatological conditions, the time at which biopsies are obtained during evolution of the eruption must be considered in the interpretation. In the case of GVHD, later stage sampling may demonstrate melanocyte damage indistinguishable from vitiligo, which may have contributed to differences in histopathologic findings in our cohort. Skin-directed therapies, such as topical steroids, topical calcineurin inhibitors, and nbUVB, are considered first-line treatments for both vitiligo and cutaneous GVHD, yet only two patients in our review reported a clinical response, reflecting the refractory nature of these pigmentary skin changes. The negative impact that pigmentary changes have on quality of life in pediatric patients, especially those of darker skin phenotypes, may lead to long-term functional and emotional impairment.[22]

Characterizing pigmentary skin changes in patients after HSCT is challenging, and the myriad clinical and histopathologic findings in patients with vitiligo-like changes suggest multiple etiologies may contribute to a shared end-manifestation of depigmentation. There are limitations to our study as our review was derived from case reports and series, which are subject to publication bias, and without a control group for comparison. Although we observed patterns within our cohort, these findings must be followed by larger, cohort-based studies that are powered to evaluate for statistical significance. Furthermore, this entity has been difficult to summarize in the literature as the nomenclature has been inconsistent; therefore, we propose use of the term "vitiligo-like" in lieu of "vitiligo" in this setting. Improved characterization of vitiligo-like changes in population-based studies may lend insight into immunologic mechanisms and therefore treatment strategies for both vitiligo and GVHD.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Totani A, Amin H, Bacchi S, Lewis I. Vitiligo following stem-cell transplant. *Bone Marrow Transplant*. 2020;55:332-340.
2. Bae JM, Choi KH, Jung HM, et al. Subsequent vitiligo after hematopoietic stem cell transplantation: a nationwide population-based cohort study from Korea. *J Am Acad Dermatol*. 2017;76:459-463.
3. Zuo RC, Naik HB, Steinberg SM, et al. Risk factors and characterization of vitiligo and alopecia areata in patients with chronic graft-vs-host disease. *JAMA Dermatol*. 2015;151(1):23-32.
4. Huang JT, Song JS, Hawryluk EB, et al. Nonmalignant late cutaneous changes after allogeneic hematopoietic stem cell transplant in children. *J Am Acad Dermatol*. 2018;79(2):230-237.
5. Nagler A, Goldenhersh MA, Levi-Schaffer F, Bystryn JC, Klaus SN. Total leucoderma: a rare manifestation of cutaneous chronic graft-versus-host disease. *Br J Dermatol*. 1996;134(4):780-783.
6. Jacobsohn DA, Ruble K, Moresi JM, Vogelsang GB. Rapid-onset leukoderma associated with graft-versus-host disease. *Bone Marrow Transplant*. 2002;30(10):705-706.
7. Cho SB, Roh MR, Chung KY, Lee KH, Park YK. Generalized vitiligo after allogeneic bone marrow transplantation. *Acta Derm Venereol*. 2005;85(1):82-83.
8. Cathcart S, Morrell D. Vitiligo as a post-bone marrow transplantation complication. *J Pediat Oncol*. 2007;29(7):485-487.
9. Mellouli F, Ksouri H, Dhouib N, et al. Possible transfer of vitiligo by allogeneic bone marrow transplantation: a case report. *Pediatr Transplant*. 2009;13(8):1058-1061.
10. Heath CR, Burk CJ, Lawley LP, Mancini AJ, Connelly EA. Severe combined immunodeficiency (SCID)-associated dyschromia with subsequent repigmentation: a report of two patients. *Pediatr Dermatol*. 2009;26(2):162-168.
11. Fukumoto M, Murao K, Watanabe H, Kubo Y, Arase S. Generalized hypopigmented macules after bone-marrow transplantation. *Clin Exp Dermatol*. 2011;36:803-804.
12. Miura T, Yamamoto T. Post-herpetic vitiligo in an 8-year-old boy with immunosuppression. *J Dermatol*. 2014;41:270-271.
13. Sheu J, Saavedra AP, Degar BA, et al. Bone marrow engraftment and associated dermatologic sequelae in a three-yr-old after liver transplantation. *Pediatr Transplant*. 2015;19:E41-E46.
14. Nambudiri VE, Tsiaras WG, Schmidt BA, Huang JT. Total leukoderma and leukotrichia in a child after hematopoietic SCT: report of a case and review of the literature. *Bone Marrow Transpl*. 2014;49:460-462.
15. Oiso N, Kawada A. Vitiligo and remarkable freckles in chronic graft-versus-host disease. *Eur J Dermatol*. 2016;26:91-92.
16. Gálvez K, Muñoz P, Vera V, Arce C. Vitiligo type cutaneous manifestation of chronic graft-versus-host disease: case report. *Rev Chil Pediatr*. 2018;89(1):113-117.
17. Radeva JI, VanScoyoc E, Smith FO, Curtis LH, Breitfeld PP. National estimates of the use of hematopoietic stem-cell transplantation in children with cancer in the United States. *Bone Marrow Transplant*. 2005;36:397-404.
18. Randolph SSB, Gooley TA, Warren EH, Appelbaum FR, Riddell SR. Female donors contribute to a selective graft-versus-leukemia effect in male recipients of HLA-matched, related hematopoietic stem cell transplants. *Blood*. 2004;103:347-352.
19. Sanli H, Akay BN, Arat M, et al. Vitiligo after hematopoietic cell transplantation: six cases and review of the literature. *Dermatology*. 2008;216:349-354.
20. Au WY, Yeung CK, Chan HH, Lie AK. Generalized vitiligo after lymphocyte infusion for relapsed leukaemia. *Br J Dermatol*. 2001;145(6):1015-1017.
21. Halder RM, Grimes PE, Cowan CA, Enterline JA, Chakrabarti SG, Kenney JA. Childhood vitiligo. *J Am Acad Dermatol*. 1987;16:948-954.
22. Silverberg JI, Silverberg NB. Qualify of life impairment in children and adolescents with vitiligo. *Peditr Dermatol*. 2014;31(3):309-318.

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