Cutaneous graft-versus-host disease within chronic photodamaged skin: A case series demonstrating role for topical 5-fluorouracil

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a major limitation to hematopoietic stem cell transplantation (HSCT), with a high mortality rate and significant financial burden on the U.S. health care system, with estimated treatment cost of 527 million USD per year.[1-3] The skin is the most common affected organ in cGVHD, present in >90% of cases[4]; additionally, it is often the first organ to be affected, foreshadowing disease in other systems.[5]

Classic dermatologic subtypes include lichenoid, sclerotic, psoriasiform, eczematous, angiomatosis, and pemphigoid-types among many others.[6-9] Persistent fibrosis and pigmentation changes are common in this population, which cause severe physical and cosmetic deformities that are distressing to the transplant recipients.[10,11] The treatment options for cutaneous cGVHD (ccGVHD) have expanded considerably in recent years.[12] There is no universal treatment in ccGVHD, which reflects the differences in pathologic processes that can lead to these skin findings. Topical and systemic corticosteroids, ruxolitinib, and belumosudil are all standard treatments of ccGVHD.[13] Skin-directed therapies provide an invaluable tool in cases of limited disease or where an adjuvant therapy is necessary. However, >50% of patients require secondary treatment options within 2 years of initial treatment.[1]

Abbreviations used:

5-FU:	5-fluorouracil
AK:	actinic keratosis
cGVHD:	chronic graft-versus-host disease
ccGVHD:	cutaneous chronic graft-versus-host disease
GVHD:	graft-versus-host disease

A previous report has discussed an actinic keratosis-like papulosquamous form of ccGVHD.[10,14] In this manuscript, we expand on this rare location and morphology of ccGVHD in which disease inhabits areas of skin with chronic photodamage, supporting the hypothesis that a high keratinocyte mutational burden in these areas leads to graft recognition and clinical GVHD. Topical 5-fluorouracil (5-FU) was used in these patients, with considerable clinical and patient-reported improvement.

All patients herein gave consent to the authors for treatment and have signed consent for photography on file with the clinic they were seen in. However, in this case, we do not believe this is applicable as we carefully chose images to demonstrate this finding that did not include facial features, jewelry, or tattoos to potentially identify patients.

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Table I. Characteristics of patient's identified with photo-distributed chronic cutaneous graft-versus-host disease

	Age (years)	Sex	Race	Disease	Graft source / sex relation / HLA match	TBI	aGVHD Prophylaxis	Sclerotic GVHD	Location	5-Fluorouracil	Clinical morphology	Pathology
1	60	M	White	MF	PB / match / URD / Full	N	Tac, MTX	Y	Chest, arms, legs	Y	AKs	Lichenoid, Keratinocyte Atypia
2	59	F	White	DLBCL	PB / - / URD / full	Y	-	Y	Head, chest	Y	AKs	n/a
3	53	M	White	FL	PB / match / URD / full	N	Tac, MTX	Y	Chest, arms	Y	AKs, sclerotic	n/a
4	70	M	White	MF	PB / match / URD / full	N	Tac, MTX	Y	Chest, legs	Y	AKs	n/a
5	66	F	White	AML	PB / mismatch / sibling / full	N	Tac, itacitinib	N	Chest, arms, legs	Y	AKs	Lichenoid, Keratinocyte Atypia
6	60	M	White	AML	PB / match / sibling / -	N	Tac, Prednisone	Y	Chest, legs	No follow-up	Sclerotic	Sclerotic, Keratinocyte Atypia
7	61	M	White	MDS	PB / mismatch / sibling / full	Y	Tac	Y	Head, chest, arms, legs	Y	AKs, sclerotic	n/a
8	52	F	White	MDS	PB / mismatch / URD / partial	N	Tac, MTX	N	Head, legs	Y	AKs	Keratinocyte Atypia, Hyperkeratosis, and Follicular Plugging
9	43	F	White	ALL	PB / match / sibling/ full	Y	Tac, MTX	Y	Chest, arms, legs	Y	AKs, sclerotic	Ulcer and granulation tissue
10	67	F	White	AML	PB / mismatch / URD / full	N	Tac, MTX	Y	Chest, legs	Y	AKs, lichenoid	Lichenoid, Keratinocyte Atypia
11	69	M	White	AML	PB / match / sibling / full	N	Tac, itacitinib	N	Head, arms, legs	Y	AKs, sclerotic	Keratinocyte Atypia
12	68	F	White	MF	PB / mismatch / child / partial	N	Tac, MMF, CP	N	Chest, arms	Y	AKs, lichenoid	Keratinocyte Atypia, Spongiotic Dermatitis
13	62	M	White	BPDCN	PB / mismatch / sibling / full	N	Tac, MTX	Y	Head, chest, arms	Y	AKs, sclerotic	Spongiotic Dermatitis

Continued

Table I. Cont'd

	Age (years)	Sex	Race	Disease	Graft source / sex relation / HLA match	TBI	aGVHD Prophylaxis	Sclerotic GVHD	Location	5-Fluorouracil	Clinical morphology	Pathology
14	41	M	White	ALL	PB / match / URD / full	Y	Tac, MTX	Y	Head, chest, arms	Y	AKs, sclerotic	n/a
15	50	M	White	AML	PB / mismatch / URD / full	Y	Tac, MTX	N	Head	Y	AKs, sclerotic	Interface Dermatitis +/- Phototoxic Eruption
Summary	58 (9.2)	60% Male	100% White	AML (33%), MF (20%), MDS (13%); ALL (13%)	100% peripheral blood, 47% matched, 47% URD, 73% full	40%	60% Tac, MTX	66.7% Y	100% photodistributed	93%	47% AKs, sclerotic	70% keratinocyte atypia, 30% lichenoid (67% of total patients biopsied)

aGVHD, Acute graft-versus-host disease; *AK*, Actinic keratosis; *ALL*, acute lymphoblastic leukemia; *AML*, acute myeloid leukemia; *BPDCN*, blastic plasmacytoid dendritic cell neoplasm; *CP*, cyclophosphamide; *DLBCL*, diffuse large B-cell lymphoma; *GVHD*, graft-versus-host disease; *HLA*, human leukocyte antigens; *MDS*, myelodysplastic syndrome; *MF*, myelofibrosis; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *PB*, peripheral blood; *Tac*, Tacrolimus; *TBI*, total body irradiation; *URD*, unrelated donor.

CASE SERIES

Demographic and clinical data were collected on a cohort of patients seen at an academic dermatology clinic over the past 5 years (2017−2021). All patients were post−allogeneic HSCT and had identified ccGVHD preferentially involving photodamaged skin.

Fifteen patients were identified and demographics are described in Table I; all patients had documented cutaneous photodamage before diagnosis. The most common affected areas of the initial presentation are listed in Table I. The physical examination showed a similar diffuse poikilodermatous pattern and scattered adherent scale with an erythematous base, which was more prominent on the sun-exposed areas of the trunk and portions of the extremities, with or without underlying sclerosis (Fig 1). Biopsy samples featured sclerotic changes and lichenoid infiltrates, most with dermatoheliosis and atypical keratinocytes (Fig 2). Clinical morphologies and pathologies are summarized in Table I. Sclerotic features of cGVHD were documented in 10 (67%) of 15 patients and noted at a median of 16.7 (SE = 9.8) months after transplant. In 4 (40%) of 10 patients, sclerosis developed in all areas of prior photodamage, and 100% of patients developed sclerosis in at least 1 photodamaged area.

Topical 5-FU 5% cream was prescribed to 14 of the patients for a 3- to 4-week treatment course at once daily application, with documented adherence to treatment and follow-up physical examinations in 7 of these patients. A total of 4 (57%) of 7 patients required 2 cycles of 5-FU for adequate improvement, with an average treatment time of 23.6 (SE = 3.9) days per cycle with an example response in Fig 3. Of these 14 patients, 10 were receiving at least 1 systemic immunomodulatory therapy at the time of treatment with 5-FU, including prednisone (8), ruxolitinib (4), tacrolimus (2), and gilteritinib (1). Of note, one patient was receiving psoralen plus UV-A during 5-FU usage, and another patient had previously undergone extracorporeal photopheresis.

DISCUSSION

ccGVHD can manifest as a myriad of cutaneous changes; however, most classically an early lichenoid, and a later sclerodermoid subtype predominate. The lichenoid subtype appears earlier and manifests as violaceous papules and plaques, nail dystrophy, mucosal ulcerations, and poikiloderma, and the sclerodermoid subtype includes morphea, lichen sclerosus-like lesions, and fascial changes.[11,15]

cGVHD is driven by the activation of the innate and adaptive immune response within a

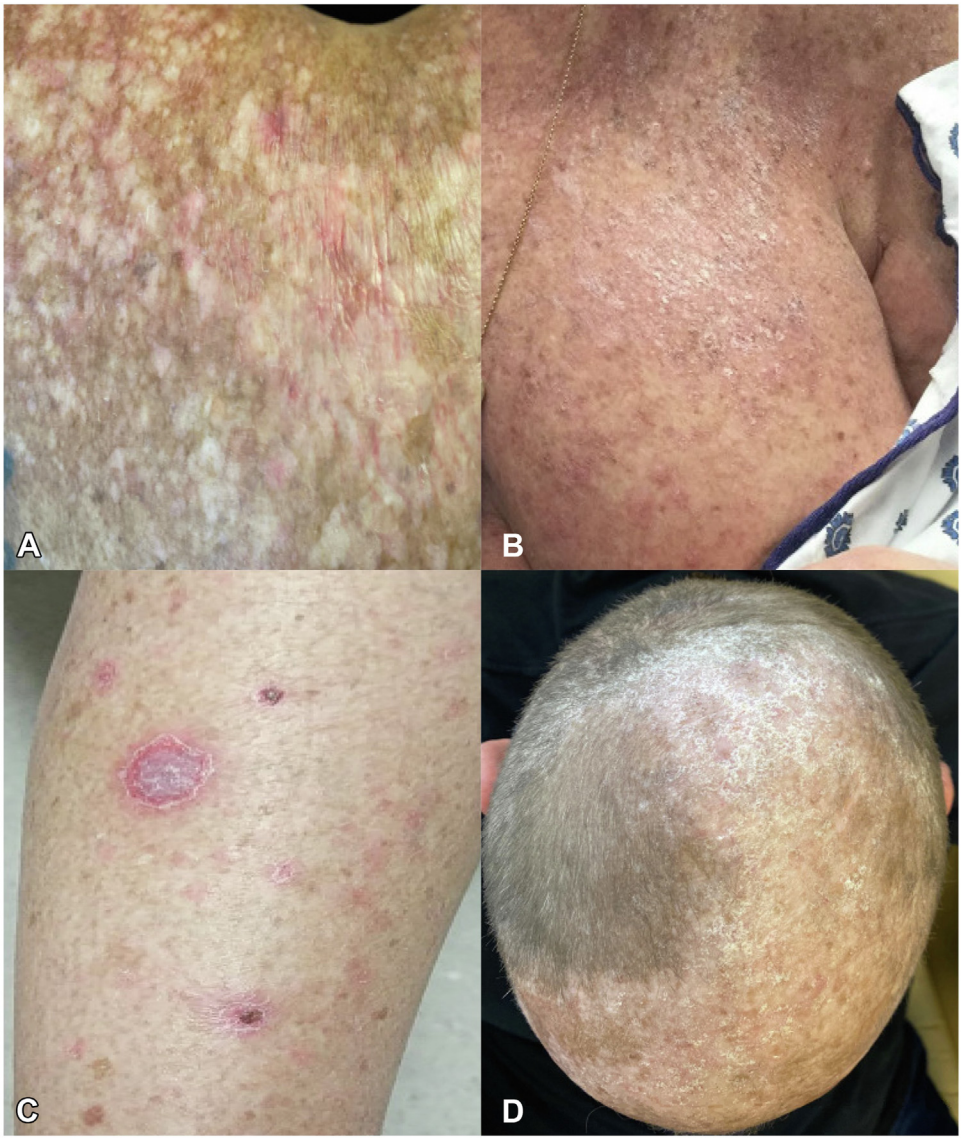

Fig 1. Clinical presentation demonstrating photodistributed poikilodermatous chronic graft-versus-host disease. (**A**) Diffuse scaling, hyperpigmentation, and thickening of skin with mottling appearance, interestingly only in sun-exposed surfaces of the skin as shown on right side of the upper portion of the back. (**B**) Red, crusty patches with slight thickening on left side of the chest with diffuse actinic keratoses. (**C**) Scattered pink papules with slight scale and superficial excoriation overlying a well-circumscribed annular plaque on the right side of the leg. (**D**) Diffuse scaling, hyperpigmentation, and thickening in mottled skin on scalp.

dysregulated central and peripheral immune system, leading to aberrant tissue repair. Chronic UV irradiation to the skin induces rare molecular signatures of keratinocytes in chronic photodamaged skin.[16] Thus, we hypothesize that chronic photodamaged skin initiates alloreactive immune response formation against rare epitopes and keratinocyte intraepithelial neoplasia with aberrant tissue repair mechanisms.

An in vitro GVHD model demonstrated increased DNA damage, loss of *TP53*, and shortened telomere length, which all contribute to development of cancers like squamous cell carcinoma.[17] Normal keratinocytes surrounding a squamous cell carcinoma have also been found to have decreased telomere length, which leads to chromosomal instability and aneuploidy development.[17-19] Decreased telomeres are associated with other inflammatory conditions with malignant

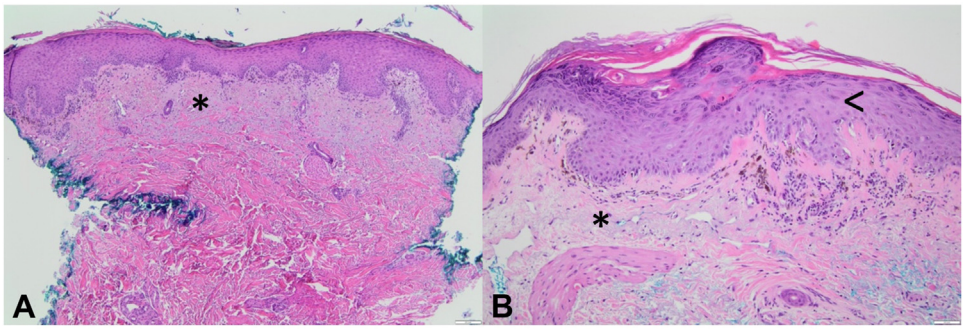

Fig 2. Lichenoid cutaneous chronic graft-versus-host disease histologic examples showing irregular epidermal hyperplasia associated with vacuolization of the dermoepidermal junction with dyskeratotic keratinocytes (arrow) and melanophages, a lichenoid lymphocytic infiltrate, and underlying dermatoheliosis (asterisks) in one patient. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A,** ×40; **B,** ×100).

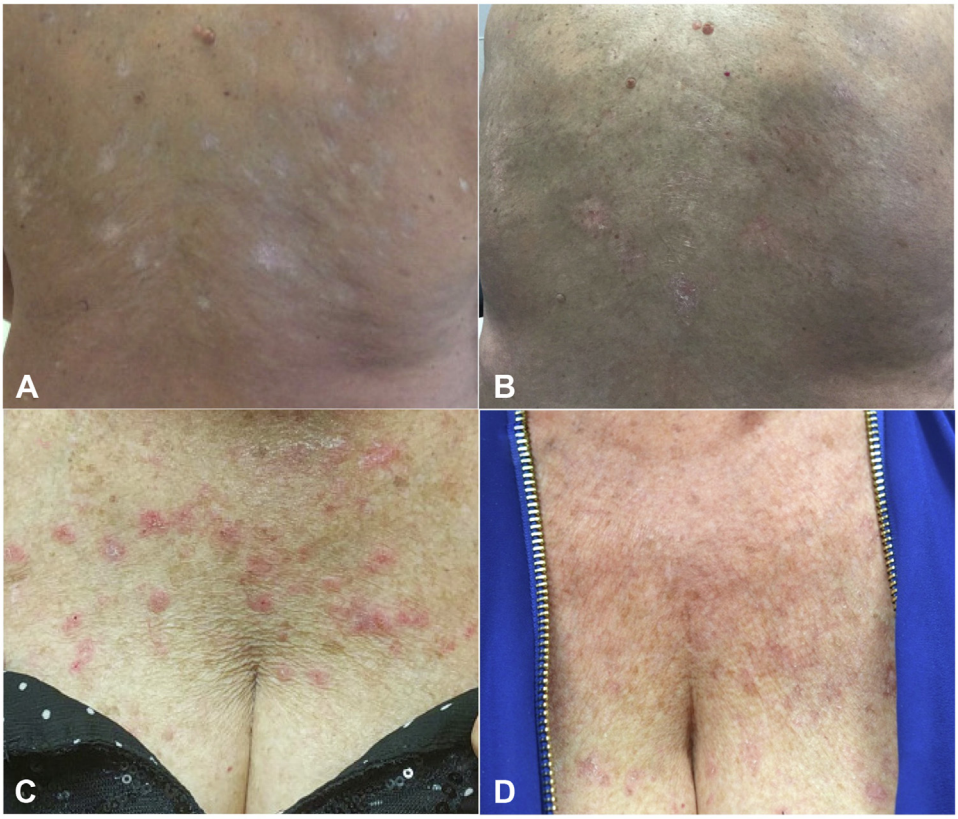

Fig 3. Photodistributed graft-versus-host disease before and after treatment with 5-fluorouracil. (**A**) Bilateral aspect of the midback of a man in his 60s with history of myelodysplastic syndrome demonstrating extensive actinic keratoses and diffuse thickening with hyperpigmented crusted plaques scattered on bilateral aspect of the midback. (**B**) Decreased number and severity of graft-versus-host disease papules and plaques on back following treatment with 5-fluorouracil for 6 weeks. (**C**) Chest of a woman in her 60s with history of mycosis fungoides demonstrating scattered pink papules with slight scale and superficial excoriation. (**D**) Decreased number and severity of graft-versus-host disease papules on chest following treatment with 5-fluorouracil for 4 weeks.

potential, such as ulcerative colitis and Barrett esophagus.[20,21] Keratinocytes in GVHD also have a greater number of tetraploid cells than normal-appearing skin, with inflammation correlating to this increase in chromosomal abnormalities in GVHD.[17] These keratinocytes then function as accessory cells in immune activation, with the ability to directly prime naïve skin-reactive $CD8^+$ T cells.[22] Keratinocytes also have the capability to stimulate humoral responses as clinical studies show antibodies to cell surface antigens in the serum of HSCT recipients with cGVHD.[23] These pathways support our hypothesis that photodamage, characterized by increased mutational burden and inflammation, initiates a cascade contributing to GVHD development.

Topical 5-FU has been available for over 5 decades and functions through DNA/RNA interference, inducing epidermal injury, and dermal remodeling, which is particularly therapeutic in photodamaged and photoaged skin.[24] Our study proposes a novel role for 5-FU in GVHD management within photodamaged skin regions. Lichenoid ccGVHD may have features that overlap with actinic damage and particularly inflamed/lichenoid actinic keratoses (AKs). The presence of scattered dyskeratosis, with or without lichenoid inflammation, would more favor ccGVHD than AKs. Additionally, although ccGVHD may have reactive cytologic atypia, the atypia would not be expected to have the nuclear pleomorphism frequently seen in AKs. Atypia in AKs is furthermore frequently associated with hypogranulosis and parakeratosis, features not generally associated with ccGVHD. However, we acknowledge the possibility that some patients have concomitant lichenoid AKs and GVHD that improves with 5-FU. Clinical involvement in our patient cohort was abrupt, diffuse, and coalescent within sun-exposed areas, which is distinct from the scattered and insidious development of AKs. Further, improvement was demonstrated in pigmentation and infiltration, not just scale, as seen with AKs treatment.

In conclusion, we report a consistent group of patients with ccGVHD who had disease isolated to areas of chronic photodamage, and several of whom responded well to topical 5-FU. Further molecular characterization of this patient subset is needed to confirm the association of abnormal keratinocyte epitopes that may drive cutaneous GVHD in this population. Future studies should be performed to confirm mutational burden present in control skin compared with photodamage-associated ccGVHD and more rigorously assess the benefit of topical antineoplastics in this setting, associations with voriconazole exposure, and long-term disease implications.

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Conflicts of interest

None disclosed.

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