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Severe acute cutaneous only graft-*versus*-host disease after late relapse of chronic myeloid leukemia and ultraviolet B phototherapy

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Title

Severe acute cutaneous only graft-*versus*-host disease after late relapse of chronic myeloid leukemia and ultraviolet B phototherapy

Running Head

Severe skin GVHD after late CML relapse and UVB

Authors

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Disclosures

No conflicts of interest to disclose.

Contributions

JSB, RP, KMA, ACMM, DAP, and JFD took part in clinical treatment and assessment of the patient. KV analyzed skin biopsies. JSB, DAP, and JFD wrote the manuscript. All authors critically assessed and approved the final manuscript.

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Data Sharing Statement

The original data and protocols pertaining to this case are available from the corresponding author upon reasonable request.

Main Text

Allogeneic hematopoietic cell transplantation (allo-HCT) is a curative therapy for leukemias, but has significant morbidity including transplantation-related mortality. Acute graft-*versus*-host disease (GVHD) is a common life-threatening complication after allo-HCT, where donor T cells recognize recipient antigens as foreign and initiate an immune response against recipient epithelial cells expressing the antigen (primarily in the skin, gut, and/or liver)[1,2]. Immunosuppression reduces acute GVHD risk, but increases serious infectious risk and reduces graft-versus-leukemia (GVL) activity. Prior to *BCR::ABL1* tyrosine kinase inhibitor (TKI) development, allo-HCT was the only curative therapy for individuals with chronic myeloid leukemia (CML), due largely to powerful GVL[3–5]. However, allo-HCT is now sparingly used in CML due to superior efficacy and safety of *BCR::ABL1* TKIs, though it remains the only curative option in TKI intolerance or advanced disease[3,4]. Herein, we present a case of severe acute cutaneous GVHD after late relapse of CML with mixed chimerism and ultraviolet B-light (UVB) phototherapy for suspected lichen planus.

A 45-year-old woman was diagnosed with chronic phase CML in 2003 and treated with all available *BCR::ABL1* TKIs over 7 years due to intolerance. She underwent allo-HCT in May 2010 due to poor quality of life on TKI therapy using myeloablative conditioning (total body irradiation, thiotepa, fludarabine, antithymocyte globulin); a CD34-selected (T-cell depleted) peripheral blood graft from a 36-year-old male 7/10 matched unrelated donor (HLA-B, -C, and -DQ mismatched) due to poor donor search; and no GVHD prophylaxis. The post-transplant course was complicated by CMV duodenitis and possible stage 1 cutaneous acute GVHD (papular, erythematous facial and upper chest rash) which resolved after a short course of prednisone 20 mg. Day 100 bone marrow (BM) biopsy showed full donor chimerism and no *BCR::ABL1* by FISH. She started maintenance dasatinib in December 2010 due to *BCR::ABL1* BM PCR positivity (0.014%). By 2018 she was in complete molecular remission off dasatinib without acute or chronic GVHD, prompting oncology clinic discharge. Routine CBC in 2019 remained normal.

In May 2023 she presented to primary care with several days of a pruritic erythematous rash on trunk and thighs. Topical triamcinolone was prescribed, but the rash spread, leading to dermatologic evaluation on 6/14/2023. Skin biopsies of the erythematous scaling plaques and papules were felt to represent lichen planus. She was treated with oral prednisone for 2 weeks with mild improvement; followed by minocycline, doxycycline, and metronidazole without benefit. By 7/13/2023, the rash covered 80% of body surface and was severely pruritic. CBC demonstrated significant leukocytosis (white blood count $49x10^9$/L), severe thrombocythemia (platelet count $1323x10^9$/L), and anemia (hemoglobin 11.5 g/dL). The differential demonstrated an absolute increase in neutrophils ($31.6x10^9$/L), basophils ($2.4x10^9$/L), and monocytes ($1.5x10^9$/L); with no increase in blasts. Narrowband UVB phototherapy three times weekly was initiated and she referred back to oncology clinic.

She re-established oncology care on 7/20/2023; when BM biopsy was performed and hydroxyurea 2 grams daily was started. The BM was hypercellular with marked myeloid and

megakaryocytic hyperplasia, without any increase in blasts, consistent with relapsed chronic phase CML. FISH showed *BCR::ABL1* rearrangement in 96% of nuclei and STR studies identified <5% donor cells. The acquisition of a new complex karyotype on metaphase cytogenetics and mutations in myeloid neoplasm driver genes including: ASXL1 (E1015Rfs*; variant allele frequency [VAF] 32%), RAD21 (P355L; 29%), and SMC1A (Q994R; 45%); were consistent with clonal evolution. Skin biopsy on 7/20/2023 showed a prominent lichenoid type, dermo-epidermal lympho-histiocytic infiltrate with scattered dyskeratotic keratinocytes within the epidermis, and dermo-epidermal junction clefting (Figure 2A); and 47% donor cells by FISH (Figure 2B). Given clinical concern for cutaneous GVHD, peripheral blood chimerism studies were obtained and showed mixed chimerism with STR CD15 <5% donor and CD3 >95% donor (Figure 2C).

The patient was seen in clinic on 7/26/2023 and labs showed improving leukocytosis ($17x10^9$/L) on hydroxyurea. Asciminib 40 mg twice daily was started given an unknown *BCR::ABL1* tyrosine kinase domain mutation status (ultimately negative) and prior intolerance of ATP-pocket binding TKIs. The same day she also received a 6th UVB phototherapy treatment, which she previously tolerated and was helping with the rash (Figure 1A-B). She developed severe burning after this treatment despite being on a stable UVB dose, which her dermatologist found surprising. She reported new skin peeling and severe pain on 7/28/2023 and was prescribed prednisone 40 mg and opioids. Her pain progressively worsened over the next 3 days and was so severe she was unable to make it to clinic on 7/31/2023, prompting direct admission by EMS transportation.

She had a long 3-month hospital course. Repeat skin biopsy on admission was similar to the one from 11 days prior, except for a relatively sparse dermo-epidermal chronic inflammatory infiltrate. Both biopsies were consistent with grade 3 acute GVHD; she did not have evidence of acute GVHD outside the skin. Her acute cutaneous GVHD slowly resolved over several months with treatment including prednisone 2 mg/kg daily (with taper), ruxolitinib 10 mg BID (with taper), and intravenous immunoglobulin. She was continued on asciminib during the admission, which was reduced to 40 mg daily when ponatinib 15 mg daily was added in 10/2023 due to persistent *BCR::ABL1* PCR positivity >10% and mixed chimerism. Subsequent PCR showed significant improvement (0.36%) on dual therapy by December 2023.

This case highlights fundamental immunological principles governing immune tolerance after allo-HCT. The CML relapse likely occurred months to years before the rash onset in May 2023, indicating she lived for an extended time with a chimeric immune system functioning in harmony. This was possible due to the unique nature of her allo-HCT including use of a CD34-selected graft and occurring at an age (32 years) with some residual thymus function. Consequently, her donor T cells underwent proper thymic and extrathymic selection, thereby inducing tolerance to recipient self-antigens. This helps explain why she did not have acute or chronic GVHD at oncology clinic discharge, despite use of only a 7/10 matched unrelated donor with no GVHD prophylaxis. Her relapsed CML exhibited clonal evolution after allo-HCT with acquisition of a complex karyotype and pathogenic mutation in *ASXL1*, likely contributing to relapse off TKI therapy[6,7]. The persistence of CD3 chimerism at relapse points to immune

escape also being a potential relapse mechanism in this case; it can occur due to loss of heterozygosity at HLA class I, which is primarily seen in transplants using poorly matched donors (as in this case)[8].

While the May 2023 rash was initially diagnosed as lichen planus, retrospectively it was clearly felt to be due to late onset acute GVHD with atypical features (prominent lichenoid type dermo-epidermal lympho-histiocytic infiltrate). The trigger of the initial donor T cell activation and subsequent GVHD remains unclear, but the lack of gastrointestinal or hepatic involvement points to skin-specific antigens being the alloreactive T cell target. While chimerism studies showed >95% recipient *BCR::ABL1* mutant myeloid cells in the BM, >95% donor T cells were retained in the peripheral blood, providing an explanation for GVHD occurrence despite minimal BM donor chimerism. The growing dominance of *BCR::ABL1* mutant cells in the myeloid compartment might have played a role in GVHD initiation, as *BCR::ABL1* has been shown to drive the expression of multiple antigens that induce HLA-restricted T-cell responses[9].

The sudden worsening of rash-related symptoms following UVB phototherapy and the largely unchanged skin biopsy results post-UVB points towards acute GVHD being the primary driver of the symptoms. While UVB phototherapy is efficacious for numerous inflammatory skin conditions due to its diverse immunosuppressive effects on the tissue, toxic doses of UVB phototherapy can induce excessive apoptosis of keratinocytes and dermal immune cells[10]. It is plausible this tissue injury and the subsequent inflammatory response resulted in activation of antigen-presenting cells (APCs), including both recipient and donor (e.g. long-lived tissue macrophages) derived APCs, leading to alloreactive donor T cell activation, thereby driving GVHD progression specifically in the skin directly impacted by UVB (Figure 3). Moreover, cutaneous GVHD is known to involve sun-exposed areas initially and multiple cases linking UVB exposure to development of cutaneous GVHD after allo-HCT have been reported[11,12]. Since the patient previously tolerated the UVB dose that led to burning, the introduction of hydroxyurea and asciminib may have also contributed to the skin toxicity observed. Both medications are recognized for inducing photosensitivity and could have amplified the impact of UVB exposure. Additionally, their use may have contributed to the death of *BCR::ABL1* mutant cells within the skin, thereby promoting APC activation. The patient in this report provided consent for treatment and publishing of the case in a journal, adherent with institutional policy and national ethical standards.

To the best of our knowledge, this is the first case report of late CML relapse after allo-HCT complicated by acute cutaneous GVHD. Our case highlights that combination therapy with asciminib and ponatinib can be tolerable and highly effective in heavily pretreated individuals with adverse genetic features, consistent with preclinical studies[13,14]. It also emphasizes the need for caution if considering the use of UBV phototherapy after allo-HCT, particularly in combination with medications that can cause photosensitivity (e.g. asciminib); this may become increasingly relevant with the uptick in TKI maintenance therapy after allo-HCT.

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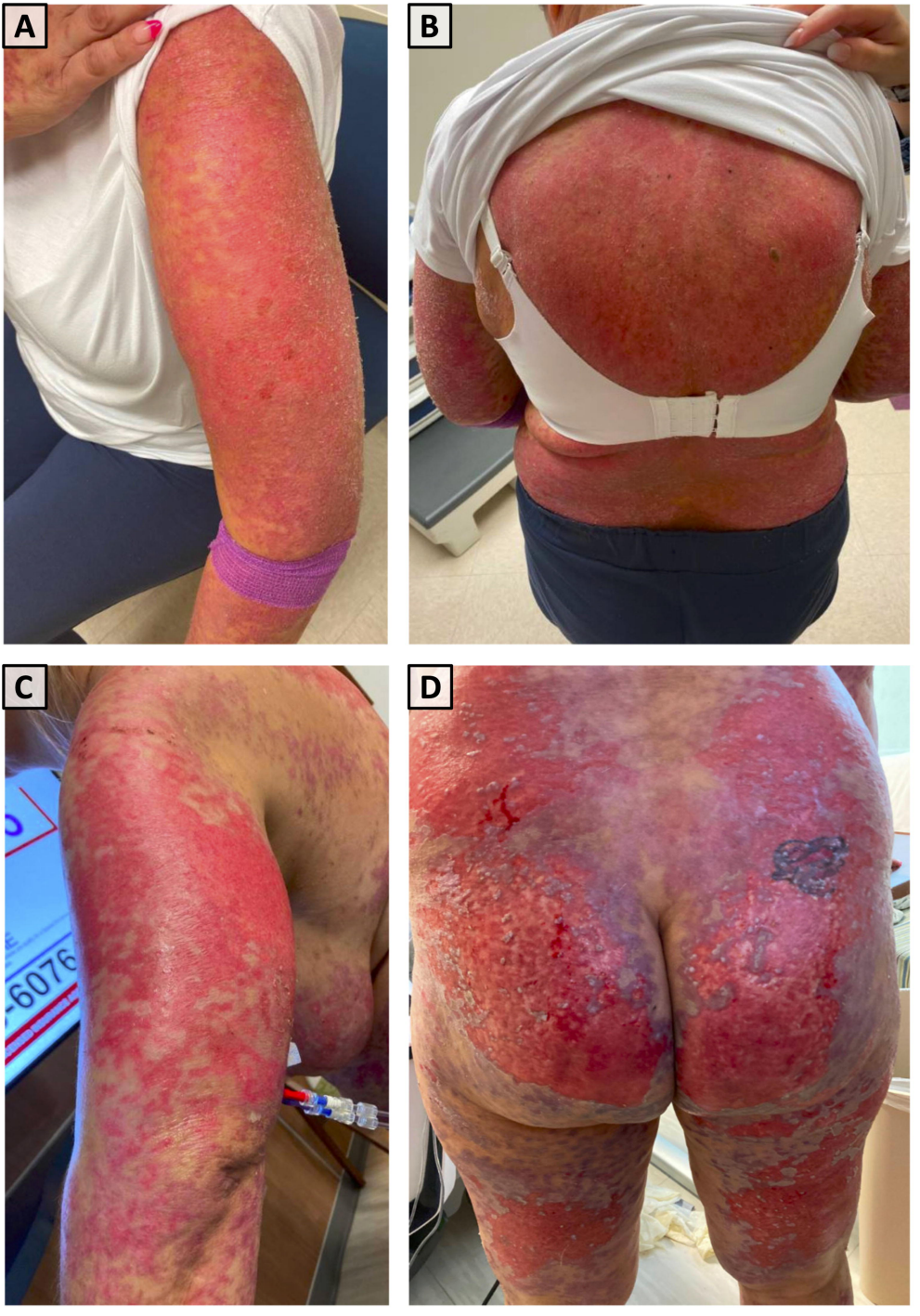
Figure Legends

Figure 1. Representative images of the diffuse erythematous rash initially diagnosed as lichen planus, but later identified as acute cutaneous GVHD. (A & B) Rash on 7/26/2023, before the onset of severe rash-associated pain. (C & D) Rash on 8/4/2023, following the onset of severe rash-associated pain.

Figure 2. Skin biopsy and chimerism analysis identify acute cutaneous GVHD in a patient with late relapse of CML with mixed chimerism after allo-HCT. (A) Right forearm skin biopsy hematoxylin and eosin (H&E) stained images at 200X (top) and 400X (bottom) magnification. The biopsy shows a lichenoid-type lympho-histiocytic infiltrate with features of grade 3 acute GVHD including: epidermal dyskeratotic keratinocytes (arrow), and dermo-epidermal interface clefting (star). (B) Fluorescence in situ hybridization (FISH) CEPXY image of the right forearm skin biopsy demonstrating 53% recipient (XX) and 47% donor (XY) cells. (C) Table presenting the donor chimerism percentage (%) stratified by sample and immune cell type at the time of the late graft failure diagnosis / CML relapse. The third column of the table is color-coded using a blue-yellow-red gradient scale.

Figure 3. Schema of the proposed immunological mechanisms underlying the events of this case report. HCT: hematopoietic cell transplant; GVHD: graft-vs-host disease; UVB: ultraviolet B; APC: antigen-presenting cell. Created in BioRender. Beeler, S. (2023) BioRender.com/q29p901.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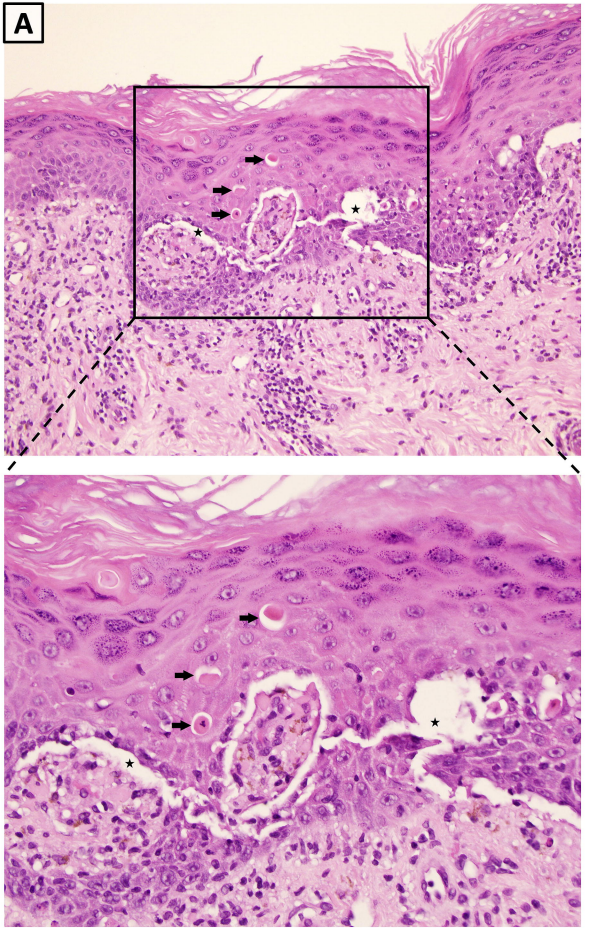

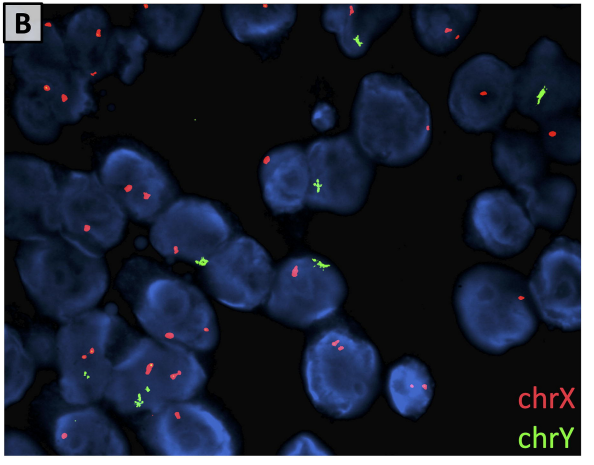

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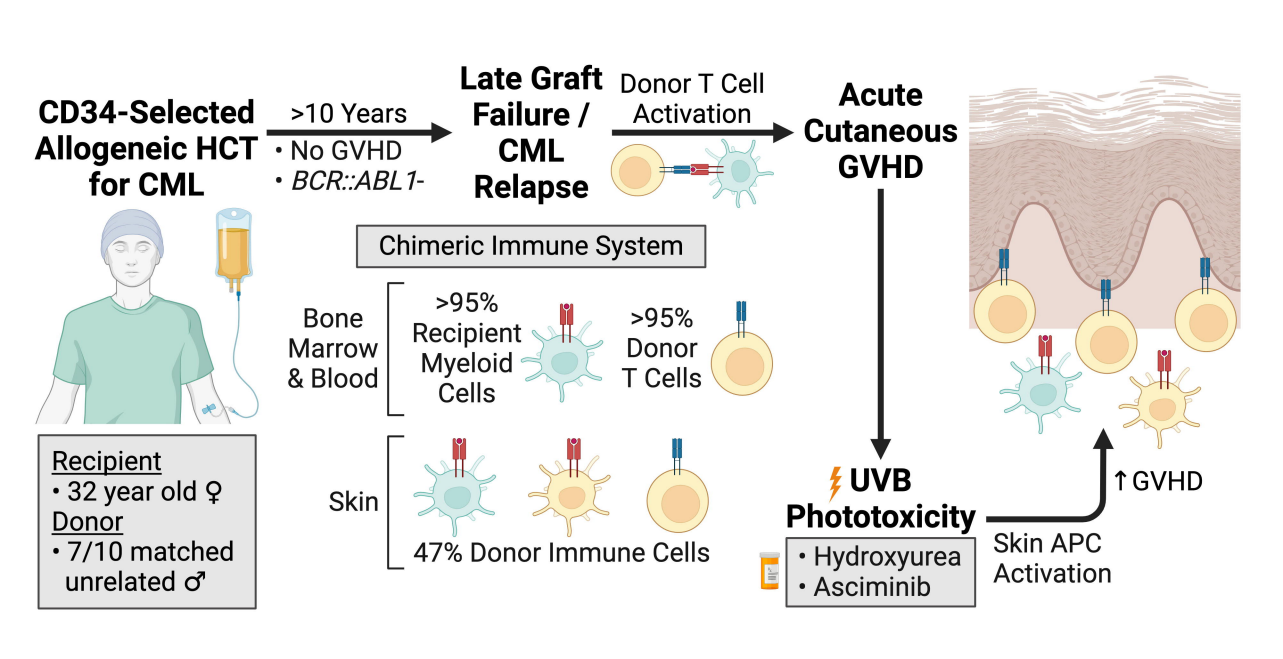
Sample	Immune Cell Type	% Donor Chimerism
Bone marrow	Pan	<5%
	CD15+ (myeloid)	<5%
	CD3+ (T cells)	>95%
Peripheral blood	CD15+ (myeloid)	<5%
	CD3+ (T cells)	>95%
Skin	Pan	47


CD34-Selected Allogeneic HCT for CML
>10 Years
• No GVHD
• BCR::ABL1-
Late Graft Failure / CML Relapse
Donor T Cell Activation
Acute Cutaneous GVHD
Chimeric Immune System
Bone Marrow & Blood
>95% Recipient Myeloid Cells
>95% Donor T Cells
Skin
47% Donor Immune Cells
Recipient
• 32 year old ♀
Donor
• 7/10 matched unrelated ♂
UVB Phototoxicity
• Hydroxyurea
• Asciminib
Skin APC Activation
↑ GVHD