Received: 9 October 2022 | Revised: 5 April 2023 | Accepted: 22 April 2023

DOI: 10.1111/cup.14444

CASE STUDY

JCP JOURNAL OF CUTANEOUS PATHOLOGY WILEY

Unusual presentations of chronic graft versus host disease

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Abstract

Skin is commonly affected by graft versus host disease (GVHD), a complication of bone marrow transplantation (BMT). One-third of hematopoietic cell transplantation recipients develop acute eruption classically described as folliculocentric, maculopapular, or morbilliform, in contrast to the more common chronic presentations of sclerotic, poikilodermic, or lichenoid dermatitides. With the wider use of non-myeloablative (reduced-intensity) transplant therapy, various atypical presentations can occur, representing a diagnostic challenge. Herein, we report an unusual case of chronic GVHD manifested by two distinct clinical and histopathological features lacking the classical presentation. Five months after her BMT, the patient presented with a papulosquamous eruption on her neck, trunk, and arms showing a psoriasiform histopathological pattern of chronic GVHD. She also demonstrated multiple small flesh-colored papules on her distal extremities showing a solitary syringotropic pattern of GVHD, demonstrated by interface dermatitis involving the superficial eccrine duct, as the only diagnostic histopathological feature of GVHD. This report, with review of literature, highlights the uncommon psoriasiform GVHD and the novel description of isolated syringotropic chronic GVHD.

KEYWORDS
eccrine duct, graft versus host disease, GVHD, psoriasiform, psoriasis, syringotropic

1 | INTRODUCTION

Graft versus host disease (GVHD) can be a complication following bone marrow transplantation (BMT) and may be a significant source of morbidity and mortality.[1] Since cutaneous presentation is the most common and usually the initial presentation, dermatologists and dermatopathologists play a crucial role in diagnosing GVHD.[2] Historically, a cut-off of 100 days post-BMT was used to define acute versus chronic GVHD.[1] However, with the introduction of pre-BMT reduced conditioning regimens, presentations of GVHD, even of acute disease, are often delayed and confounded by atypical lesions that overlap with the classic chronic picture. This prompted the National Institute of Health (NIH) Consensus Working Group on chronic GVHD to recommend using only clinical and histopathological manifestations to distinguish between the acuity and chronicity of GVHD.[3]

Although there are no strictly defined pathognomonic features for GVHD, the 2005 NIH Consensus Conference and the 2014 NIH Pathology Working Group defined the minimal histopathological criteria for active cutaneous GVHD (acute or chronic) as apoptosis within the basilar or lower spinosum layer of the epidermis.[3,4] Follicular epithelium, acrosyringium, and sweat ducts may also be affected.[3,5] In addition, the diagnosis of chronic GVHD requires at least one diagnostic feature, or a distinctive feature supported by histopathology. Diagnostic features can be comprised of sclerotic, poikilodermic, or lichenoid dermatitides. Distinctive features include but are not limited to oral ulcers, xerostomia, sicca syndrome-like changes, depigmentation, and papulosquamous lesions.[2,6,7]

There are limited descriptions of unusual presentations of cutaneous GVHD in the literature. A 2018 review paper reported one case

The authors declare that the contents of this article are their own original unpublished findings.

TABLE 1 Summary of current and previously described cases of psoriasiform GVHD.

Age and sex	Conditioning regimen	Indication/type of transplant	GVHD category/ time to onset	Personal or family history of psoriasis	Treatment/course
49 F	Fludarabine/ cyclophosphamide/TBI	AML/BMT	Chronic/150 days	No	Sirolimus/stable
62 M[a]	N/A	PMF/PBSCT	Chronic/300 days	No	Mycophenolate; intermittent prednisone/stable
40s M[b]	Fludarabine/ cyclophosphamide/ATG/ TBI	Aplastic anemia/ BMT	Chronic/380 days	No	Clobetasol ointment, ruxolitinib/ stable
47 M[c]	N/A	ALL/HSCT	Chronic/365 days	No	Methotrexate/partial remission
33 F[d]	Busulfan/fludarabine/ATG	HLH/BMT	Chronic/201 days	No	Narrow-band ultraviolet B /stable
40 M[e]	Fludarabine/ cyclophosphamide/3 courses of CHOP	CLL/PBSCT	Late-onset acute/200 days	Not reported	Extracorporeal photochemotherapy, mycophenolate, cyclosporine/ continuous remission
4 M[f]	N/A	ALL/BMT	Acute/60 days	No	Methotrexate/continuous remission
18 months F[g]	N/A	AML/BMT	Late-onset acute/191 days	No	Psoralen/topical steroids, calcineurin inhibitors/ progression to sclerosis
30 F[h]	Busulfan/fludarabine/ATG	Marginal zone lymphoma/ PBSCT	Acute/34 days	No	Psoralen/continuous remission
40 M[i]	Ciclosporin/methotrexate/ ATG	T-lymphoblastic leukemia	Chronic/1140 days	No	Secukinumab/anti-interleukin-17A antibody/stable

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; BMT, bone marrow transplant; CHOP, cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), prednisone; CLL, chronic lymphocytic leukemia; D, days; F, female; GVHD, graft versus host disease; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem-cell transplantation; M, male; N/A, not applicable; PBSCT, peripheral blood stem cell transplant; PMF, primary myelofibrosis; TBI, total body irradiation.

[a]Vernali et al.[8]
[b]Milam et al.[10]
[c]Chasset et al.[11]
[d]Jang et al.[12]
[e]Sirinoglu Demiriz et al.[13]
[f]Taguchi et al.[14]
[g]Kawakami et al.[7]
[h]Matsushita et al.[9]
[i]Debureaux et al.[15]

and summarized seven reported cases of acute and chronic psoriasiform GVHD.[8] To date, only nine total cases of psoriasiform GVHD have been described, including a recent case reported in 2020 (Table 1).[7–15] Absence of sweat glands, dilation of secretory glands, and squamous metaplasia are common findings described as features of eccrine involvement in chronic GVHD, but these are often found in association with other classic clinical and histopathological features of GVHD.[5] Herein, we report the simultaneous occurrence of two unusual presentations of chronic GVHD in a 49-year-old female 5 months after her BMT: psoriasiform and isolated syringotropic patterns. We aim to highlight the importance of keeping these atypical subtypes in the differential diagnosis for patients who receive hematopoietic cell transplantation, especially if conditioned with reduced-intensity chemoradiotherapy. We also review the literature for plausible explanations of psoriasiform GVHD in BMT recipients with no prior personal or donor history of psoriasis.

2 | CASE SYNOPSIS

A 49-year-old female with no personal or family history of psoriasis presented with a 5-day history of numerous red, pruritic, mildly edematous papules and plaques without scales (Figure 1A). Her medical history was significant for acute myeloid leukemia (AML) treated with matched unrelated donor allogeneic stem cell transplantation 44 days prior to the onset of cutaneous lesions. In preparation for BMT, the patient was conditioned with a non-myeloablative regimen of fludarabine, cyclophosphamide, and total body irradiation (Table 1). She was admitted for suspected grade 3 acute GVHD and stabilized with prednisone, methylprednisolone, and sirolimus. A punch biopsy from the right forearm showed mild interface lymphocytic inflammation involving the epidermis, acrosyringium, and superficial eccrine ducts, associated with scattered necrotic keratinocytes, supporting the clinical impression of acute GVHD (Figure 1B–D). After 11 days of high-dose

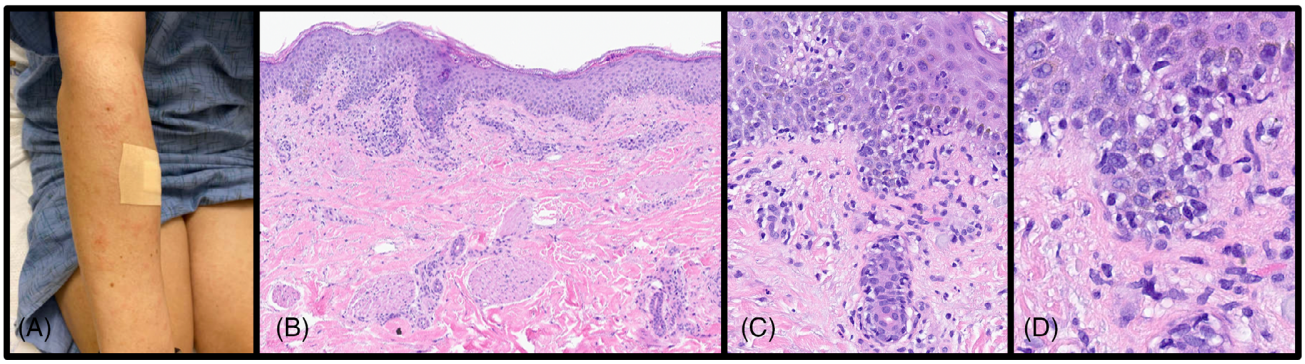

FIGURE 1 Acute graft versus host disease. Numerous red, pruritic, mildly edematous papules and plaques without scaling on the upper extremities (A). Histopathology shows interface dermatitis with scattered necrotic keratinocytes involving the epidermis (B, 100×), the acrosyringium and the superficial portion of eccrine duct in the papillary dermis (C, 200× and D, 400×).

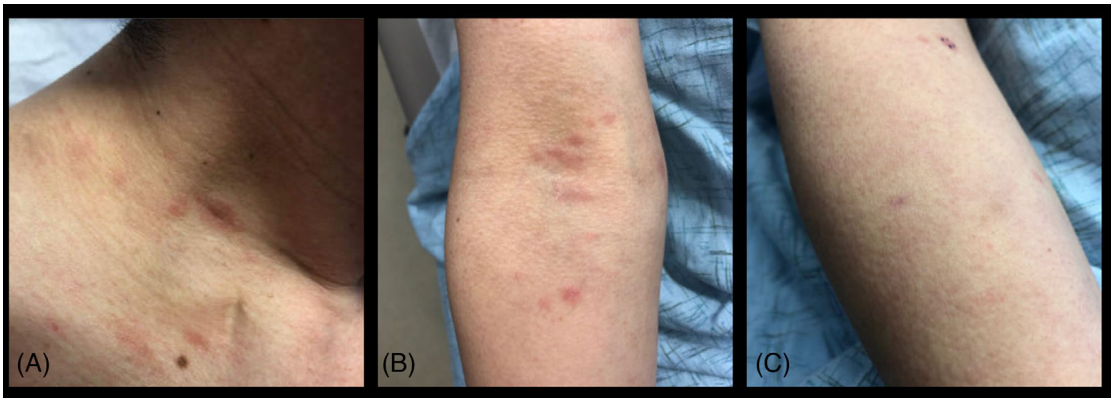

FIGURE 2 Chronic graft versus host disease. Thin pink ovoid papules and plaques scattered on her chest, neck (A), and right forearm (B). Extensive flesh-colored flat-topped papules on her distal extremities (C).

systemic steroids, she was discharged on sirolimus, ruxolitinib, and prednisone. Ruxilitinib and prednisone were tapered off in the outpatient setting while sirolimus was continued.

Five months post-transplantation, the patient presented with newly occurring, mildly pruritic lesions with two distinct morphologic features: a papulosquamous eruption consisting of thin pink ovoid scaly papules and plaques scattered on her upper trunk and forearms (Figure 2A,B), and numerous small flesh-colored flat-topped papules on her distal extremities (Figure 2C).

In addition to the classic histopathologic findings of psoriasiform dermatitides, such as acanthosis, broad parakeratosis focally containing neutrophils, and diminution of the granular layer, a punch biopsy from her right arm also showed interface lymphocytic inflammation and rare necrotic keratinocytes, supporting a diagnosis of psoriasiform GVHD (Figure 3A–D). The patient was not on any medications with strong evidence for drug-induced psoriasis, and a significant number of eosinophils were not seen in the biopsy. A punch biopsy from her right leg showed a mild syringotropic inflammation demonstrated by interface lymphocytic inflammation involving the superficial portion of eccrine ducts in the papillary dermis, associated with dyskeratosis and mild periductal lymphocytic inflammation (Figure 3E–G). The epidermis was not involved. This syringotropic inflammation was focal and only present in one of the multiple deeper sections examined. Deep eccrine glands were not involved (Figure 3H). This patient's papulosquamous lesions, as a distinctive clinical feature of chronic GVHD confirmed by its psoriasiform GVHD features histopathologically, meet the NIH criteria for chronic GVHD. While the small flat papules on the lower extremities, showing unclassified features of GVHD demonstrated by a solitary syringotropic inflammation, cannot be used to establish an initial diagnosis of chronic GVHD based on NIH criteria, however, because of their simultaneous onset with the papulosquamous lesions, they most likely represent a second manifestation of her chronic GVDH eruption. Neither of the biopsies showed classic histopathologic features of chronic GVHD, such as lichenoid or sclerodermoid features. The sirolimus dose was doubled, which improved but did not completely clear the rash (Table 1).

3 | CASE DISCUSSION

The increased use of reduced-intensity chemotherapy conditioning treatment before BMT has led to the emergence of what is referred

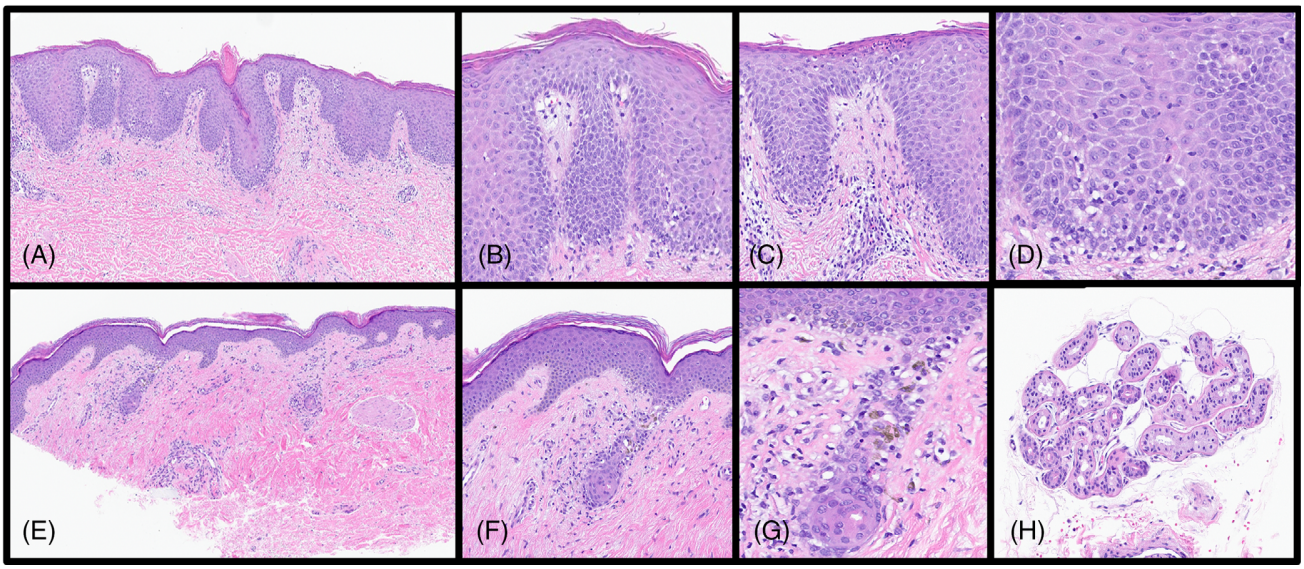

FIGURE 3 Chronic graft versus host disease. Biopsy from the right forearm shows mixed psoriasiform and interface patterns involving the epidermis and follicular epithelium (A, 40×), diminution of the granular cell layer with overlying broad parakeratosis (B, 100×) focally containing neutrophils (C, 100×). Rare necrotic keratinocytes are noted (D, 200×). Biopsy from the lower extremity shows an interface lymphocytic inflammation only involving superficial eccrine ducts in the papillary dermis (E, 40× and F, 100×), associated with dyskeratosis and a mild periductal lymphocytic inflammation (G, 200×). Deep eccrine units are not involved (H, 100×).

to as the graft versus tumor (GVT) effect, where donor adaptive immune cells, especially T-cells, can be observed eliminating residual leukemic cells. However, this non-myeloablative regimen is also responsible for delayed presentations of atypical forms of acute GVHD and the acute-chronic GVHD overlap.[1] To better categorize GVHD and guide proper management, the 2014 NIH Consensus Working Group recommended diagnostic criteria for chronic GVHD requiring at least one diagnostic clinical manifestation, or a distinctive clinical feature supported by histopathology in place of the historic post-BMT 100-day cut-off.[3]

At present, acute GVHD can be classified into subtypes such as persistent, recurrent, or late-onset, and is characterized by the eruption of morbilliform rash, erythema multiforme, or Stevens–Johnson syndrome. Alternatively, the chronic form is characterized by the presence of at least one diagnostic feature (sclerotic, poikilodermic, or lichenoid dermatitides), or a distinctive feature (oral ulcers, xerostomia, sicca syndrome-like changes, depigmentation, and papulosquamous lesions) supported by histopathology.[2,3,6,7] Unlike acute GVHD, treatment of chronic GVHD is mainly supportive, aiming at mitigating morbidities and alleviating symptoms. Therefore, distinguishing between acute and chronic presentations is crucial for proper management and avoiding unnecessary excessive immunosuppression that compromises GVT antitumor activity.[3]

We present the case of a 49-year-old female who initially presented with classic acute GVHD, which went into remission with treatment. More than 3 months later, she developed two distinct forms of chronic GVHD, with psoriasiform, and isolated syringotropic inflammation as the main histopathological feature, without typical lichenoid or sclerodermoid changes. The Working Group's definition of chronic GVHD was met, given there was one distinctive feature (papulosquamous lesions) supported by histopathology. While the syringotropic inflammation alone is not sufficient to make the diagnosis of chronic GVHD, its simultaneous presentation with psoriasiform lesions supports the diagnosis.

Only nine cases of psoriasiform GVHD have been reported in the literature (Table 1).[7–15] None of the cases reported a personal or family history of psoriasis. Existing literature shows that patients with no history of psoriasis developed psoriasis after receiving allogeneic BMT from donors with psoriasis, and patients' psoriasis resolved following allogeneic BMT from donors with no history of psoriasis. These findings suggest an adoptive transfer of susceptibility from a donor with a psoriatic genetic background.[16–19] However, the lack of similar history in psoriasiform GVHD prompts the need for an alternative explanation.

One possible hypothesis proposes the similarity in immunopathogenesis between psoriasiform chronic GVHD and psoriasis, accounting for the comparable clinical and histopathological features. This theory is supported by the findings of similar cytokine profiles in the psoriasiform chronic GVHD lesions demonstrating an infiltrate predominated by IFN-γ-producing Th1 cells and IL-17-producing Th17 cells.[15] Another possible explanation is that excess donor lymphocytic interaction triggers recipient keratinocytic proliferation resulting in a histopathological pattern similar to psoriasis.[8] Our patient had no prior medical history of psoriasis, and the fact that she and other reported cases received reduced-intensity conditioning treatment before their BMT lends credibility to the latter theory.[9,10,12]

GVHD causing eccrine gland abnormalities has been well documented.[5,6] Lymphocyte infiltration of eccrine glands with subsequent syringometaplasia and anhidrosis has been commonly described in acute GVHD.[20] Complete eccrine gland destruction associated with

squamous metaplasia and fibrosis has been observed in chronic GVHD.[5] Syringotropic inflammation in acute and chronic GVHD is often associated with other classic diagnostic features, such as an interface lymphocytic inflammation and apoptosis in the epidermis or follicular epithelium in acute GVHD, and lichenoid or sclerotic changes in chronic GVHD.[5] To our knowledge, the isolated presentation of our patient's small flat-topped papules on distal extremities with histopathologic features of isolated superficial syringotropic interface inflammation is a novel finding of this report. Among the nine reported cases of psoriasiform GVHD, syringotropic interface lymphocytic inflammation with rare apoptotic keratinocytes involving the acrosyringium was described in one case.[8] This was seen in the same biopsy specimen showing psoriasiform features. Lymphocyte activation has been reported in cases with both psoriasiform and syringotropic GVHD. Cytokine induction from activated lymphocytes may lead to psoriasiform changes and eccrine destruction. Given the small size of eccrine units, syringotropic inflammation of GVHD might be identified in more cases of psoriasiform GVHD if additional deeper sections were to be examined. Furthermore, the histopathological evidence of syringotropic GVHD was very focal in the biopsy of our patient, indicating the importance of examining multiple deeper sections.

Herein, we aimed to draw attention to the possible correlation between non-myeloablative conditioning treatment and the emergence of unusual GVHD presentations. We, too, call attention to the importance of maintaining a high index of suspicion for atypical cutaneous forms of chronic GVHD in patients with a history of BMT and the significance of obtaining a biopsy to confirm or exclude GVHD, especially when mimickers like psoriasis are often diagnosed clinically without the need for histopathologic examination.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No data sharing needed.

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How to cite this article: Okorie CL, Salem I, Scripture AJ, Simmons BJ, Momtahen S, Yan S. Unusual presentations of chronic graft versus host disease. *J Cutan Pathol*. 2024;51(1):15-19. doi:10.1111/cup.14444