Reactivated chronic graft-versus-host disease following SARS-CoV-2 infection

Brian Florenzo, BS, BA,[a] Seth Martin, MD,[b] and Arturo Saavedra, MD, PhD, MBA[b]

Key words: COVID-19; graft-versus-host disease; immunodermatology; infectious diseases; SARS-CoV-2; stem cell transplant.

INTRODUCTION

Graft-versus-host disease (GVHD) continues to be a common complication of hematopoietic stem cell transplants (SCTs), affecting up to 40% to 60% of patients.[1] While acute GVHD has largely been associated with aberrant donor T-cell response, chronic GVHD (cGVHD) is thought to be a more complex reaction involving multiple immune cell lineages. Cutaneous GVHD is known to sometimes flare following modulations in treatment or recent infection.[2-4] However, to our knowledge, no cases of cGVHD reactivation secondary to coronavirus disease 2019 (COVID-19) have yet been reported in the literature. We present here a case of cutaneous cGVHD flaring in the setting of SARS-CoV-2 infection.

CASE REPORT

Our patient was a 51-year-old African American male with a history of stage IV Waldenstrom's macroglobulinemia and lymphoplasmacytic lymphoma treated with matched-related allogeneic SCT 2 years prior. His SCT had been complicated by skin-limited cGVHD previously stable for greater than a year. He presented to our dermatology clinic with a 9-day history of a painful, pruritic rash on his hands and feet that soon spread over his shoulders and back. He had no constitutional complaints and no other organ involvement, and his integumentary system was otherwise negative on review. One week prior to the onset of cutaneous symptoms, the patient had been diagnosed with COVID-19.

Abbreviations used:

GVHD:	graft-versus-host disease
cGVHD:	chronic graft-versus-host disease
COVID-19:	coronavirus disease 2019
SCT:	stem cell transplant

A physical examination revealed annular violaceous-to-erythematous papules and plaques with peripheral scale scattered over the torso, and most prominently over the lower back and shoulders (Fig 1). Similar papules were also noted on dorsal hands and in the interdigital space of the first and second fingers bilaterally. On the plantar surfaces of both feet, there were deep-seated pseudovesicles with small rims of scale that were exquisitely tender to palpation (Fig 2). No other associated mucocutaneous findings were identified. Initial differential diagnosis was broad and included lichen planus, scabies, lichenoid GVHD, pityriasis rosacea, syphilis, and granuloma annulare.

Characteristic papules on the patient's left foot and lower back were biopsied, which revealed lichenoid dermatitis with prominent pigment incontinence. Satellite cell necrosis in the form of dyskeratotic keratinocytes was noted throughout the epidermis and the follicular epithelium, while spirochete immunohistochemical and PAS stains revealed no organisms (Fig 3). Given these clinical and histological findings, the patient was diagnosed with chronic lichenoid grade II GVHD.

From the Department of Dermatology, University of Virginia School of Medicine, Charlottesville, Virginia[a]; and Department of Dermatology, University of Virginia Medical Center, Charlottesville, Virginia.[b]

Funding sources: None.

IRB approval status: Not applicable.

Consent: Consent for the publication of all patient photographs and medical information was provided by the authors at the time of article submission to the journal stating that all patients gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

Correspondence to: Arturo Saavedra, MD, PhD, MBA, Department of Dermatology, University of Virginia Medical Center, 1221 Lee St, 3rd Floor, Charlottesville, VA 22903. E-mail: AS4DA@hscmail.mcc.virginia.edu.

JAAD Case Reports 2022;26:76-8.

2352-5126

https://doi.org/10.1016/j.jdcr.2022.06.015

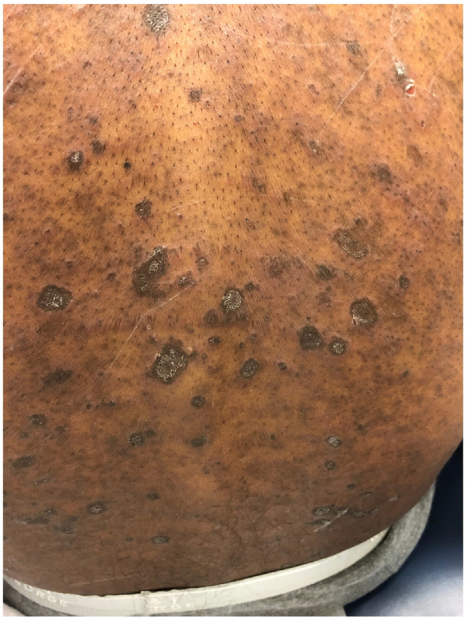

Fig 1. Annular violaceous-to-erythematous papules located throughout the back.

In collaboration with his oncology team, he was initiated on a prednisone taper starting at 70 mg that was slowly tapered over the course of 5 months. During the first month of treatment, he was concurrently given betamethasone 0.1% ointment under occlusion along with urea 40% cream on the palms and soles. After 1 month of minimal improvement this regimen, ruxolitinib 10 mg BID was initiated, which resulted in significant improvement in his symptoms over the succeeding 4-6 weeks. By 3 months after initiating the medication, he was able to taper the ruxolitinib down to 2.5 mg BID with intermittent use of topical triamcinolone 0.1% for mild flares. At 6-month follow up, his cutaneous GVHD remains quiescent with ruxolitinib and intermittent topical steroid use.

DISCUSSION

GVHD remains a significant side effect of SCT, and upward of 30% to 70% of patients who experience GVHD go on to develop chronic manifestations of the disease.[3] Cutaneous eruptions are often the most common and earliest presenting manifestations of GVHD and can include poikiloderma, lichen planus–like skin changes, sclerosis, morphea-like features, depigmentation, pruritus, maculopapular rash, papulosquamous lesions, and erythema.[2] While the exact pathophysiology of cGVHD remains enigmatic, there is a general consensus that cGVHD arises as the result of an abnormal cycle of tissue damage leading to the release of inflammatory mediators which in turn

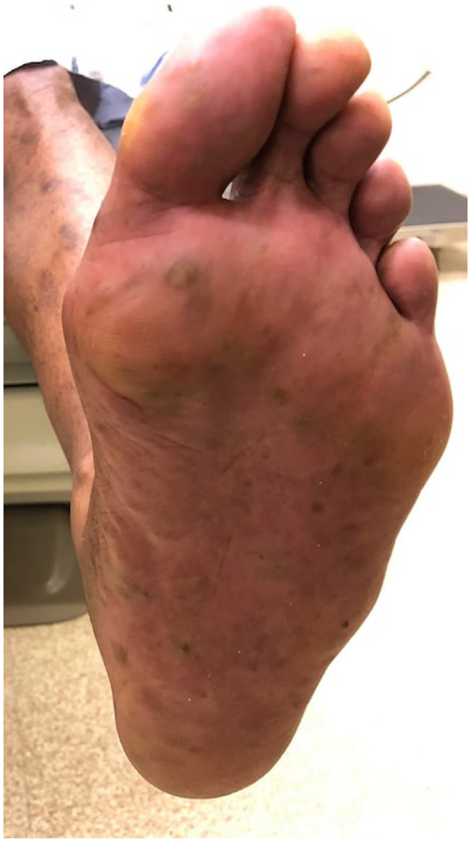

Fig 2. Deep-seated plantar pseudovesicles with slight scaled rims.

promote a hyper-reactive response by the adaptive immune system to host foreign major histocompatibility complex proteins. This, combined with a general reduction of regulatory immune cells and abnormal fibroblast activation, leads to many of the symptoms associated with cGVHD.[2,3] In the context of this case, the rapid reactivation of previously remittent cGVHD following SARS-CoV-2 infection implies that the inflammatory environment created by the virus in conjunction with the subsequent immune response can promote and amplify the aberrant processes seen in pre-existing cGVHD.[5,6] While our understanding of this virus continues to evolve, numerous reports in the literature have described other cases in which COVID-19 has been implicated in the development of other cutaneous conditions associated with immune dysregulation such as systemic lupus erythematosus,[7] pansclerotic morphea,[6] alopecia areata,[8] pustular psoriasis,[9] as well as a multitude of nonspecific rashes.[10]

Despite its atypical clinical presentation, the cGVHD flare associated with this case was able to be effectively treated using the standard agents employed for severe disease—systemic glucocorticoids,

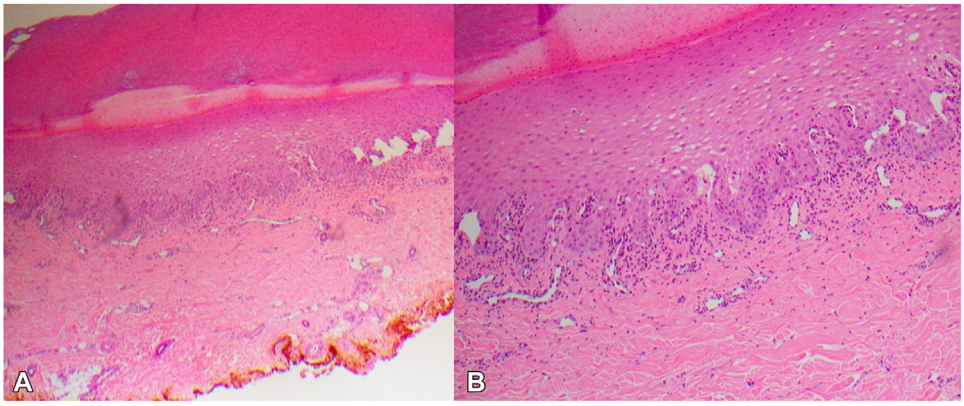

Fig 3. Histopathology at 40× (**A**) and 100× (**B**) demonstrating a lichenoid interface dermatitis with dyskeratotic keratinocytes within the epidermis. Eosinophils are not readily identified.

ruxolitinib, and topical emollients.[2] Other potential treatment options that were not used but have previously been demonstrated to be effective against cGVHD include extracorporeal photopheresis, calcineurin inhibitors, rituximab, and symptomatic alleviation as deemed appropriate.[4]

Research regarding the relationship between specific viruses and GVHD remains scarce, and to our knowledge, there has been no previous association between cGVHD and COVID-19. Given the ubiquitous and persistent nature of the virus, it is imperative that dermatologists and other clinicians working with SCT patients are aware of this rare association given its severity and significant impact on prognosis. The constellation of symptoms presented in the case appeared concurrently with the patient's COVID-19 diagnosis; however, it is unclear whether this temporal course is case-specific or more generalizable to the population-at-large. With that in mind, individuals with a history of cGVHD should be followed up closely after a diagnosis of COVID-19, as is the case after other infections, in order to implement early and affective therapies should they flare. Subsequent follow-up needs remain unclear given the novelty of the association and should be based on individualized provider-patient risk discussions.

In conclusion, we present a case of reactivated cGVHD following SARS-CoV-2 infection. Cutaneous manifestations included erythematous papules and plaques with peripheral scale across the torso in addition to deep seated pseudovesicles on the plantar surfaces. Although rare, it is important for clinicians to have a low index of suspicion for this condition following COVID-19 infection to avoid delays in diagnosis and treatment for this potentially lethal complication.

Conflicts of interest

None disclosed.

REFERENCES

1. Strong Rodrigues K, Oliveira-Ribeiro C, de Abreu Fiuza Gomes S, Knobler R. Cutaneous graft-versus-host disease: diagnosis and treatment. *Am J Clin Dermatol*. 2018;19(1):33-50. https://doi.org/10.1007/s40257-017-0306-9
2. Ramachandran V, Kolli SS, Strowd LC. Review of graft-versus-host disease. *Intersect Dermatol Oncol*. 2019;37(4):569-582. https://doi.org/10.1016/j.det.2019.05.014
3. Zeiser R, Blazar BR. Pathophysiology of chronic graft-versus-host disease and therapeutic targets. *N Engl J Med*. 2017;377(26):2565-2579. https://doi.org/10.1056/NEJMra1703472
4. Cutler CS, Koreth J, Ritz J. Mechanistic approaches for the prevention and treatment of chronic GVHD. *Blood*. 2017;129(1):22-29. https://doi.org/10.1182/blood-2016-08-686659
5. Caso F, Costa L, Ruscitti P, et al. Could Sars-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? *Autoimmun Rev*. 2020;19(5):102524. https://doi.org/10.1016/j.autrev.2020.102524
6. Lotfi Z, Haghighi A, Akbarzadehpasha A, Mozafarpoor S, Goodarzi A. Pansclerotic morphea following COVID-19: a case report and review of literature on rheumatologic and non-rheumatologic dermatologic immune-mediated disorders induced by SARS-CoV-2. *Front Med*. 2021;8:1799. https://doi.org/10.3389/fmed.2021.728411
7. Zamani B, Moeini Taba SM, Shayestehpour M. Systemic lupus erythematosus manifestation following COVID-19: a case report. *J Med Case Rep*. 2021;15(1):29. https://doi.org/10.1186/s13256-020-02582-8
8. Capalbo A, Giordano D, Gagliostro N, et al. Alopecia areata in a COVID-19 patient: a case report. *Dermatol Ther*. 2021;34(2):e14685. https://doi.org/10.1111/dth.14685
9. Assan F, Sbidian E, Bachelez H. Response to "New-onset pustular psoriasis in the setting of severe acute respiratory syndrome coronavirus 2 infection causing coronavirus disease 2019.". *JAAD Case Rep*. 2021;11:130-131. https://doi.org/10.1016/j.jdcr.2021.02.024
10. Drenovska K, Schmidt E, Vassileva S. Covid-19 pandemic and the skin. *Int J Dermatol*. 2020;59(11):1312-1319. https://doi.org/10.1111/ijd.15189