

Delayed presentation of toxic epidermal necrolysis-like cutaneous acute graft-versus-host disease in the setting of recent immunosuppressant discontinuation.

Parul Kathuria Goyal MD, Shuai Xu MD, MSc, Jennifer Choi MD

Affiliations: Department of Dermatology, Northwestern University, Chicago, Illinois

Corresponding Author: Jennifer Choi MD, Northwestern University Department of Dermatology, 676 N St. Clair, Suite 1600, Chicago, IL 60611, Email: jennifer.choi@northwestern.edu

Abstract

Acute graft-versus-host disease (GvHD) is a process that classically has been defined as occurring less than 100 days after stem cell transplant. When Stage IV cutaneous acute GvHD occurs outside this window, it can be difficult to distinguish clinically from toxic epidermal necrolysis (TEN). A 50-year-old man with diffuse large B-cell lymphoma who had undergone an allogeneic stem cell transplant 20 months previously was admitted for neutropenic septic shock. He developed a slowly progressing macular/papular eruption with multiple tender bullae found to be consistent with TEN-like Stage IV cutaneous acute GvHD on biopsy. It was discovered that the patient's maintenance immunosuppression had been completely discontinued one month prior to admission in preparation for clinical trial enrollment, causing a late presentation of cutaneous acute GvHD. This case provides particular insight into the diagnosis and management of late-presenting acute GvHD given that it is the first reported case of Stage IV cutaneous acute GvHD more than 12 months after stem cell transplant. In the setting of decreased immunosuppression in a patient with a history of a stem cell transplant, acute graft-versus-host disease must be considered regardless of the time that has elapsed since transplant.

Keywords: acute graft-versus-host disease; toxic epidermal necrolysis mimickers; chronic lymphocytic leukemia

Introduction

Acute graft-versus-host disease (GvHD) is a known complication of hematopoietic stem cell transplant previously thought to present primarily within the first 100 days after stem cell transplant, although reports exist in the literature of acute GvHD presenting after this time period. Here we report a case of Stage IV TEN-like acute cutaneous GvHD occurring after 100 days post-stem cell transplant in the setting of a recent decrease in immunosuppression. This case is of particular clinical interest given that to our knowledge, it is the first case describing a Stage IV acute GvHD skin reaction more than one year after allogeneic hematopoietic stem cell transplant.

Case Synopsis

A 50-year-old man with chronic lymphocytic leukemia (CLL) transformed to diffuse large B-cell lymphoma (DLBCL) two years previously was admitted for neutropenic septic shock. The dermatology team was consulted to evaluate a cutaneous eruption first noticed two weeks previously after the administration of quetiapine that persisted after quetiapine was switched to olanzapine. Over the past day, the primary team had noted new-onset multiple tender fluid-filled bullae over his bilateral forearms shortly after the initiation of amikacin, aztreonam, vancomycin, and metronidazole.

The patient's oncologic history consisted of a diagnosis of CLL transformed to DLBCL approximately two years previously. He underwent several rounds of chemotherapy and ultimately received a matched unrelated donor stem cell transplant 20 months prior to current presentation. He developed Stage I cutaneous GvHD that was managed by his



Figure 1. initial presentation of stage IV cutaneous acute graft-versus-host disease. From left to right: morbilliform eruption over chest; erosion with denuded skin on right arm; two fluid-filled bullae marked for biopsy.

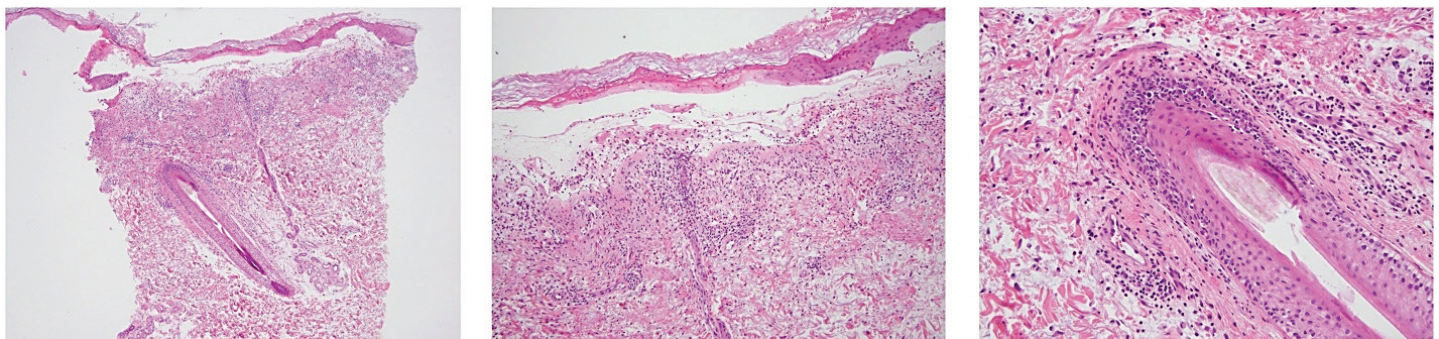


Figure 2. Lichenoid process involving skin adnexa with extensive superficial epidermal necrosis suspicious for graft-versus-host disease from a 4-mm punch biopsy. From left to right: low power view revealing a necrotic epidermis with clefting and subepidermal bulla formation; higher power view revealing scattered inflammatory cells within the bulla and upper dermis with focal exocytosis of lymphocytes and dermal edema with mixed inflammatory infiltrate; and lichenoid adnexal inflammation with satellite cell necrosis. H&E, 4%, 10% and 20%, respectively.

oncologist three months after transplant. He was then found to have recurrent DLBCL eight months prior to current presentation but had no response to further chemotherapy and was scheduled to be enrolled in the CAR-T (chimeric antigen receptor-T cell) trial. CAR-T therapy re-engineers patients' own T cells to produce CD19-targeted chimeric antigen surface receptors that recognize and attack tumor cells. In preparation for enrollment, his maintenance immunosuppression (tacrolimus, rituximab, lenalidomide) was discontinued one month prior to current presentation.

Dermatologic examination revealed nearly confluent erythematous macules and papules overlying the bilateral arms and trunk with discrete, fully blanchable macules and papules over the bilateral legs. On the right upper arm, there was an erosion with denuded skin four centimeters in diameter. Three fluid-filled bullae two centimeters in diameter were noted on the left upper arm (**Figure 1**). The mucosal surfaces

and palms and soles were clear.

A 4-mm lesional punch biopsy of a left upper arm lesion revealed a subepidermal necrotic bulla with lichenoid inflammation of the skin adnexa and extensive satellite cell necrosis noted to be consistent with toxic epidermal necrosis (TEN)-like acute graft-versus-host disease. Stevens-Johnson syndrome and erythema multiforme were also in the differential diagnosis (**Figure 2**). A 4-mm perilesional punch biopsy sent for direct immunofluorescence showed no significant activity.

The patient was treated with 1 mg/kg of intravenous methylprednisolone for four days and with topical corticosteroids to affected skin twice daily. His methylprednisolone dose was then increased to 2 mg/kg for an additional four days, completing a total of eight days of intravenous corticosteroids. He was then transitioned to oral prednisone 60 mg twice daily for two days and discharged on oral prednisone



Figure 3. resolution of stage IV cutaneous acute graft-versus-host disease. From left to right: patient's left arm with dry exfoliative scale and resolution of previous erythema and bullae; abdomen clear of lesions.

50 mg twice daily. Repeat dermatologic examination seven days later showed resolution of the eruption with no new bullae formation (**Figure 3**). Two weeks after discharge, the patient developed a severe infection and ultimately passed away.

Case Discussion

Acute graft-versus-host disease is a donor T cell mediated process in which donor T cells are activated against host antigens after allogeneic hematopoietic stem cell transplant. Activated effector T cells then migrate to the gut, liver, skin, lung, and lymphoid tissue and cause local tissue destruction [1]. Acute GvHD was classically thought to occur within 100 days after stem cell transplant [2]. There is, however, a growing body of literature that discusses acute GvHD presenting after this time frame [3-5]. Holtan et al. defined this entity as late acute GvHD, performing the first prospective analysis of over 900 patients who developed symptoms of acute graft-versus-host disease greater than 100 days after hematopoietic cell transplant [6]. In cutaneous acute GvHD, skin lesions begin as erythematous macules and papules that coalesce into papules and plaques two to six weeks after transplant. The first lesion often begins around a hair follicle, with lesions appearing on the cheeks, neck, back, and palms and soles before spreading to the entire body. After initial presentation, the skin desquamates and may leave post-inflammatory changes [2].

Four clinical stages of cutaneous acute GvHD have been delineated. Stage I is defined as a macular/

papular rash involving 25 percent of body surface area (BSA) or less. Stage II is defined as a macular/papular rash involving 25 to 50 percent BSA. Stage III is generalized erythroderma, whereas Stage IV is defined by toxic epidermal necrolysis-like appearance with total dermatoepidermal separation visualized on dermatopathology [2]. Current studies of patients with cutaneous acute GvHD

have shown that approximately 2% of cases will be classified as Stage IV disease [7].

Per this staging system, our patient had Stage IV acute GvHD. Although his disease manifested after 100 days post-transplant, he had acute disease clinically and histologically. Our patient's maintenance tacrolimus, rituximab, and lenalidomide had been discontinued one month prior to his presentation in preparation for enrollment in the CAR-T trial. Given that the patient had already had a mild episode of cutaneous graft-versus-host disease three months after his stem cell transplant, the recent decrease in immunosuppression likely triggered a flare of acute GvHD despite the unusual time course. This phenomenon of GvHD of this severity erupting immediately after a reduction in immunosuppression has not been described in the existing literature to our knowledge. In 2001, Valks et al. described a series of three patients in whom clinical and pathological features of acute GvHD developed greater than 100 days after peripheral blood stem cell transplant or allogeneic bone marrow transplant. All patients had a flare of grade II acute GvHD that occurred after tapering their prophylactic regimens of cyclosporine in combination with either methotrexate or corticosteroids [3]. Later that year, Wollina et al. described a case of a 40-year-old woman who had a peripheral blood stem cell transplant in September 1998 who presented nine months later with stage I acute graft-versus-host disease within one week of her prophylactic prednisone dose being tapered [4]. Our case is unique from those which were previously

published and of particular clinical interest given the severity, rapid onset, and extensive nature of our patient's GvHD.

First-line therapy for the treatment of grades II to IV acute GvHD is IV methylprednisone started at a dose of 2 milligrams/kilogram/day [8]. A meta-analysis looking at augmentation of 2 mg/kg prednisone with higher doses of corticosteroids, infliximab, antithymocyte globulin, mycophenolate mofetil, CD5-specific immunotoxin, and anti-IL2 receptor Ab found no increased efficacy with the addition of a second immunosuppressant [9]. High potency topical corticosteroids can be used in isolation for patients with stage I cutaneous acute GvHD with no evidence of systemic involvement [10]. Lastly, phototherapy has been shown to be useful for clearing cutaneous GvHD, but further data is needed to fully characterize its use [11].

Our patient initially responded well to therapy, but Stage IV cutaneous acute GvHD portends an extremely poor prognosis in the literature. In one study detailing fifteen cases of Stage IV cutaneous acute GvHD, thirteen patients (87%) died within 12 months, with the median time of death from onset of disease being 33 days. Causes of death included pulmonary GvHD, CMV infection, sepsis, pneumonia, GI bleed, hepatic failure, hemorrhage, GvHD involving the CNS, acute leukemia, and endocarditis. Of these thirteen patients, five of them had cleared their cutaneous acute GvHD at time of death with corticosteroids and other immunosuppressants. The two patients alive at the end of the study had also recovered from their cutaneous disease [12]. Similarly, our patient had cleared his cutaneous GvHD at the time of his death and ultimately died from an infection.

Minimal literature exists characterizing the difference in outcomes between patients presenting with early-versus late-onset acute GvHD of all types. In one study among patients with late-onset acute GvHD, defined as acute GvHD presenting greater than 100 days after transplant, 52% had acute GvHD that persisted, 39% had recurrent disease, and 9% had de novo disease. At two years, more patients with late acute GvHD had progressed to chronic GvHD compared to early acute GvHD (48% versus 31%). Overall survival, however,

was higher in late acute GvHD when compared to early acute GvHD (59% versus 50%). Lastly, unrelated donor transplantations were associated with a higher risk of mortality in patients with late acute GvHD as compared to early acute GvHD, with the hazard ratio being 6.1 [13].

Conclusion

Ultimately, in the setting of decreased immunosuppression in a patient who has had a stem cell transplant at any time point, acute graft-versus-host disease must be considered in the differential diagnosis.

References

1. Socie G, Blazar BR. Acute graft-versus-host disease: from the bench to the bedside. *Blood*. 2009;114(20):4327-36. Epub 2009/08/29. [PMID: 19713461].
2. Penas PF, Zaman S. Many faces of graft-versus-host disease. *The Australasian journal of dermatology*. 2010;51(1):1-10; quiz 1. Epub 2010/02/13. [PMID: 20148830].
3. Valks R, Fernandez-Herrera J, Bartolome B, Fraga J, Dauden E, Garcia-Diez A. Late appearance of acute graft-vs-host disease after suspending or tapering immunosuppressive drugs. *Archives of dermatology*. 2001;137(1):61-5. Epub 2001/02/15. [PMID: 11176662].
4. Wollina U, Sayer HG, Wollina K, Graefe T. Very late appearance of acute graft-versus-host disease after tapering immunosuppression. *The Journal of dermatology*. 2001;28(12):734-6. Epub 2002/01/24. [PMID: 11804070].
5. Vandenberghe P, Verhoef GE, Emonds MP, Demuyneck H, Zachee P, De Wolf-Peeters C, Decorte R, Cassiman JJ, Boogaerts MA. A single course of remission reinduction chemotherapy for acute myelogenous leukemia relapsing after allogeneic bone marrow transplantation is complicated by graft-versus-host disease and followed by sustained complete remission. *Leukemia*. 1997;11(10):1775-8. Epub 1997/10/27. [PMID: 9324300].
6. Holtan SG, Khera N, Levine JE, Chai X, Storer B, Liu HD, Inamoto Y, Chen GL, Mayer S, Arora M, Palmer J, Flowers ME, Cutler CS, Lukez A, Arai S, Lazaryan A, Newell LF, Krupski C, Jagasia MH, Pusic I, Wood W, Renteria AS, Yanik G, Hogan WJ, Hexner E, Ayuk F, Holler E, Watanaboonyongcharoen P, Efebera YA, Ferrara JL, Panoskaltis-Mortari A, Weisdorf D, Lee SJ, Pidala J. Late acute graft versus host disease: a prospective analysis of clinical outcomes and circulating angiogenic factors. *Blood*. 2016. Epub 2016/09/15. [PMID: 27625357].
7. Martin PJ, Schoch G, Fisher L, Byers V, Anasetti C, Appelbaum FR, Beatty PG, Doney K, McDonald GB, Sanders JE, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. *Blood*. 1990;76(8):1464-72. Epub 1990/10/15. [PMID: 2207321].
8. Martin PJ, Rizzo JD, Wingard JR, Ballen K, Curtin PT, Cutler C, Litzow MR, Nieto Y, Savani BN, Schriber JR, Shaughnessy PJ, Wall DA, Carpenter PA. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Journal of the American Society for Blood and Marrow Transplantation*. 2012;18(8):1150-63. Epub 2012/04/19. [PMID: 22510384].
9. Rashidi A, DiPersio JF, Sandmaier BM, Colditz GA, Weisdorf DJ. Steroids Versus Steroids Plus Additional Agent in Frontline

- Treatment of Acute Graft-versus-Host Disease: A Systematic Review and Meta-Analysis of Randomized Trials. *Journal of the American Society for Blood and Marrow Transplantation*. 2016;22(6):1133-7. Epub 2016/03/13. [PMID: 26970383].
10. Penas PF, Fernandez-Herrera J, Garcia-Diez A. Dermatologic treatment of cutaneous graft versus host disease. *American journal of clinical dermatology*. 2004;5(6):403-16. Epub 2005/01/25. [PMID: 15663337].
 11. Garbutcheon-Singh KB, Fernandez-Penas P. Phototherapy for the treatment of cutaneous graft versus host disease. *The Australasian journal of dermatology*. 2015;56(2):93-9. Epub 2014/10/11. [PMID: 25302552].
 12. Goiriz R, Penas P, Perez-Gala S, Delgado-Jimenez Y, Aragues M, Garcia-Diez A, Fraga J, Figuera A, Fernandez-Herrera J. Stage IV cutaneous acute graft-versus-host disease. Clinical and histological study of 15 cases. *Journal of the European Academy of Dermatology and Venereology*. 2009;23(12):1398-404. Epub 2009/06/16. [PMID: 19522707].
 13. Omer AK, Weisdorf DJ, Lazaryan A, Shanley R, Blazar BR, MacMillan ML, Brunstein C, Bejanyan N, Arora M. Late Acute Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation. *Journal of the American Society for Blood and Marrow Transplantation*. 2016;22(5):879-83. Epub 2016/01/09. [PMID: 26743342].