CLINICAL VIGNETTE

Graft-Versus-Host Disease Mimicking Tinea Corporis after Small Intestine Transplant

Sarah Lonowski, MD, MBA and Mengjun Hu, MD

Case

A 14-year-old male presented with an asymptomatic rash 7 months following small intestine transplant. His post-transplant course had been complicated by mild cutaneous graft-versus-host-disease (GVHD) 2 months after transplant, treated with steroids and sirolimus, as well as severe autoimmune hemolytic anemia, treated with high dose steroids and rituximab. The new rash began on the face, then spread to involve the trunk and extremities. The patient did report a slight increase in stool output, but he was otherwise at his baseline state of health. He had been undergoing a slow steroid taper in the month preceding the onset of the rash. The transplant physician was initially concerned about a fungal infection and the patient was started on clotrimazole cream. He was already on fungal prophylaxis with oral fluconazole 200mg daily. Dermatology was consulted and examination showed annular scaly plaques with central clearing on the face, neck, trunk, and groin. A KOH test was equivocal. Given high clinical suspicion for tinea corporis and lack of response to topical and systemic azoles, the patient was started on terbinafine cream twice daily. After one week the rash was not improving and two punch biopsies were performed.

Histopathology showed GVHD, supported by the presence of dyskeratotic/necrotic cells and superficial perivascular inflammatory infiltrate. Subsequent liver and intestinal biopsies were also consistent with GVHD. The patient was started on basiliximab as well as topical steroids, with improvement in the rash. Unfortunately, the patient had persistent infection with rhinovirus and mycoplasma and his respiratory status continued to decline. He eventually developed multi-organ failure and died after a prolonged hospitalization.

Discussion

GVHD is a well-known and common, 35-50% complication of hematopoietic stem cell transplant.[1] GVHD after solid organ transplant is much less common, although some authors believe it is likely under-diagnosed.[2] Solid organ transplant-associated GVHD has been most commonly reported after liver transplant,[3] but the risk of GVHD is actually highest among small intestine transplant recipients, with an incidence around 5%.[4,5] Other known risk factors for solid organ transplant-associated GVHD include African-American race, human leukocyte antigen mismatch, cytomegalovirus infection, multi-organ transplant, and younger age.[3.5] The relative increased risk of GVHD in small intestine transplant may be related to the high density of lymphoid tissue in this organ compared to other solid organs.[1,6]

GVHD occurs when immunocompetent donor immune cells are activated and proliferate in response to exposure to host antigens, leading to inflammation and destruction of host tissues.[7] The most common targets of these donor immune cells are the skin, liver, and intestine.[5] Rash is the most common manifestation of solid organ transplant-associate GVHD. In one study of 115 solid organ transplant patients with GVHD, dermatologic manifestations were present in 87.8% of cases and appeared on average 48 days post-transplant.[3] Rash is often the earliest clinical manifestation of GVHD, preceding liver or GI involvement.[4] The rash of solid organ transplant-associated GVHD has most commonly been described as a “maculo-papular” or “morbilliform” eruption involving the trunk, extremities, and occasionally the face, palms, and soles – often mimicking a viral exanthem or drug reaction.[3] Other presentations of cutaneous GVHD include confluent erythema, blistering and desquamation, including toxic epidermal necrolysis-like presentations.[3,5] In most cases, the rash is not pruritic.[3] To our knowledge, this is the first case of solid organ transplant-associated cutaneous GVHD that mimics tinea corporis. Other common presenting symptoms in solid organ transplant-associated GVHD include gastrointestinal symptoms and antibody-mediated hemolytic anemia; both of which were found in our patient.

Diagnosis of GVHD is based on clinical symptoms, laboratory abnormalities, and histopathologic changes in affected tissues.[1] Key histologic features of cutaneous GVHD include vacuolar interface change, dyskeratotic/necrotic keratinocytes, and a perivascular inflammatory infiltrate.[8] According to one large series, keratinocyte necrosis is the most common histopathologic finding.[5] A widely accepted scheme for histologic diagnosis of acute GVHD has been developed, with grading from 1 to 4 indicating increased severity.[5] In difficult cases, ancillary studies which demonstrate significant donor lymphoid chimerism are also available. In sex-mismatched patients, fluorescence in situ hybridization for donor lymphocytes can be performed on skin biopsy specimens.[3,8] The degree of lymphocyte chimerism in skin or GI biopsy specimens can also be assessed using DNA short tandem repeats.[8] Finally, polymerase chain reaction-based serum studies can detect a high proportion of circulating donor cells.

Steroids continue to be the first-line treatment for both acute and chronic GVHD with topical steroids for skin-limited disease and systemic steroids for multi-organ involvement. Other therapies for acute GVHD include alternative immunosuppressive agents such as mycophenolate, anti-tumor necrosis factor-alpha antibodies, and anti-interleukin-2 receptor antibodies including basiliximab, which was used on our patient.[2] For chronic GVHD, treatment depends on cutaneous morphology, with no single agent emerging as consistently superior.[7] Another seemingly paradoxical approach to the treatment of solid organ transplant-associated GVHD involves decreasing or withdrawing immunosuppression in order to restore the host immune system and enable it to fight against activated donor immune cells.[2]

Despite treatment, GVHD is associated with a high mortality rate. The mortality of acute GVHD in solid organ transplant patients has been reported to be as high as 85%.[8] Prompt recognition and diagnosis of GVHD can lead to earlier initiation of treatment and potentially save lives. This case serves as a reminder to keep GVHD high on the differential diagnosis when a patient with a history of transplant develops a rash, even if the morphology of the rash is atypical for cutaneous GVHD. This case adds to the literature for potential cutaneous manifestations of GVHD in patients that have undergone solid organ transplant.

REFERENCES

1. **Zhang Y, Ruiz P**. Solid organ transplant-associated acute graft-versus-host disease. *Arch Pathol Lab Med*. 2010 Aug;134(8):1220-4. doi: 10.5858/2008-0679-RS.1. PMID: 20670147.
2. **Sharma A, Armstrong AE, Posner MP, Kimball PM, Cotterell AH, King AL, Fisher RA, Godder K**. Graft-versus-host disease after solid organ transplantation: a single center experience and review of literature. *Ann Transplant*. 2012 Dec 31;17(4):133-9. doi: 10.12659/aot.883704. PMID: 23274334.
3. **Kim GY, Schmelkin LA, Davis MDP, El-Azhary RA, Farrell AM, Meves A, Lehman JS**. Dermatologic manifestations of solid organ transplantation-associated graft-versus-host disease: A systematic review. *J Am Acad Dermatol*. 2018 Jun;78(6):1097-1101.e1. doi: 10.1016/j.jaad.2017.12.050. Epub 2017 Dec 27. PMID: 29288097; PMCID: PMC6167008.
4. **Gulbahce HE, Brown CA, Wick M, Segall M, Jessurun J**. Graft-vs-host disease after solid organ transplant. *Am J Clin Pathol*. 2003 Apr;119(4):568-73. doi: 10.1309/395B-X683-QFN6-CJBC. PMID: 12710129.
5. **Mazariegos GV, Abu-Elmagd K, Jaffe R, Bond G, Sindhi R, Martin L, Macedo C, Peters J, Girnita A, Reyes J**. Graft versus host disease in intestinal transplantation. *Am J Transplant*. 2004 Sep;4(9):1459-65. doi: 10.1111/j.1600-6143.2004.00524.x. PMID: 15307833.
6. **Andres AM, Santamaría ML, Ramos E, Sarriá J, Molina M, Hernandez F, Encinas JL, Larrauri J, Prieto G, Tovar JA**. Graft-vs-host disease after small bowel transplantation in children. *J Pediatr Surg*. 2010 Feb;45(2):330-6; discussion 336. doi: 10.1016/j.jpedsurg.2009.10.071. PMID: 20152346.
7. **Bolognia JL, Jorizzo JL, Schaffer JV**. *Dermatology, 4th Edition*: Philadelphia, Elsevier Limited. 2018. 810-818.
8. **Patterson J**. *Weedon's Skin Pathology, 4th Edition*: Philadelphia, Elsevier Limited. 2016. 60-62.