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Dermatologic manifestations of solid organ transplantation-associated graft-versus-host disease: A systematic review

Grace Y. Kim, B.A.¹, Leah A. Schmelkin, M.D.², Mark D.P. Davis, M.D.³, Rokea A. el-Azhary, M.D.,Ph.D.³, Ann M. Farrell, M.L.S.⁴, Alexander Meves, M.D.³, and Julia S. Lehman, M.D.^{3,5}

¹Mayo Clinic School of Medicine, Rochester, MN, USA.

²Mayo Clinic School of Graduate Medical Education, Mayo Clinic, Rochester, MN, USA.

³Department of Dermatology, Mayo Clinic, Rochester, MN, USA.

⁴Mayo Clinic Libraries, Mayo Clinic, Rochester, MN, USA.

⁵Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA.

Keywords

Graft-versus-host disease; transplant; dermatopathology

INTRODUCTION

Graft-versus-host-disease (GVHD) is a multisystem disease that can occur after blood and marrow or solid organ transplantation. Transplanted immune cells (graft) recognize cells or tissues from the transplant recipient (host) as foreign and initiate an immune reaction manifesting in multiple organ systems, often including the skin. GVHD following solid organ transplantation (solid organ transplantation-associated GVHD; SOT GVHD) may present in one of two forms¹. The more common form involves an antibody-mediated reaction against the recipient's red blood cells, resulting in a mild and transient hemolytic anemia. The second form is driven by cellular immunity and may affect the recipient's skin, gastrointestinal tract, liver, and/or bone marrow¹. Known risk factors for developing SOT GVHD include: African American race, HLA mismatch, and cytomegalovirus infection², as well as an underlying tumor diagnosis or neoadjuvant chemotherapy administered before the transplant³. While 3 case reports from the literature have shown that aggressive

Corresponding author: Dr. Julia S. Lehman. 200 First Street SW, Rochester, MN, 55905. **Telephone:** 507-284-2555 **Fax:** 507-284-2072 lehman.julia@mayo.edu.

Reprint request: Dr. Julia S. Lehman. lehman.julia@mayo.edu

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immunosuppression and plasmapheresis can be successful in treating SOT GVHD, there still exist challenges to treatment^{4–6}.

Though patients with SOT GVHD may experience cutaneous involvement, it has been our experience that the associated eruption is non-specific and may mimic more common entities, such as viral exanthema or drug reaction. Lack of its recognition may lead to a delay in diagnosis and possibly worsened outcomes. We aimed to perform a systematic review on available relevant literature to better understand this rare but potentially serious complication of solid organ transplantation, with an emphasis on its dermatologic manifestations.

METHODS

Literature search

With the assistance of a Masters level medical librarian (A.F.), we performed a systematic review of existing English-language literature on patients who demonstrated dermatologic manifestations after SOT GVHD. We searched the following databases: MEDLINE (1946–2016), Embase (1988–2016), Web of Science (1975–2016), and Scopus (1823–2016). Studies published online, published in print, and in press from all years were considered. All search results with titles and abstracts written in English were eligible for inclusion. Studies were excluded based on the title, abstract, or both if there was no clear indication as to whether they documented dermatologic manifestations of graft-versus-host-disease after solid organ transplantation. Pediatric SOT GVHD cases were excluded. Due to the rare nature of SOT GVHD, case reports were included for review.

Data extraction

The following parameters were documented: first author; year of publication; number of cases reported; dermatologic features of SOT GVHD; skin symptoms; when skin symptoms first appeared after transplant; methods used to determine the diagnosis of SOT GVHD; biopsy results; organ involvement and complications; treatment regimen; patient outcome.

RESULTS

Study characteristics

The initial literature search yielded a total of 1233 articles. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is presented in Fig 1. In 61 articles published between 1991 and 2016, there were 115 patients with SOT GVHD reported. Of these patients, a total of 126 organs were transplanted, as some patients received multiple organs^{4–65}. SOT GVHD was most common after liver transplantation (n=81, 64.3%). A summary of data from existing literature can be found in Table 1.

Dermatologic manifestations

Of the 92 patients for whom the duration between transplantation and development of skin eruption was recorded, dermatologic manifestations of SOT GVHD developed an average of 48.3 days (range: 3–243^{48,60}) after transplant, which is earlier than the 63 days observed in our retrospective review of patients (n=9) at the Mayo Clinic (unpublished data). While

dermatologic findings were variable, the most frequent description was that of a maculopapular exanthem [28 of 101 (27.7%) patients], with 2 (1.9%) also being described as morbilliform^{11,23}. Confluent erythema and desquamation were observed in 6 (5.9%)^{13,17,26,44,46,57} and 4 (3.9%)^{26,50,51,63} patients, respectively. In one patient, the dermatologic symptoms initially began as a maculopapular eruption that progressed to one resembling toxic epidermal necrolysis⁶⁰. Of 101 patients, dermatologic findings involved the extremities in 16 (15.8%) , the trunk in 14 (13.9%) , and the face in 9 (8.9%). Detailed dermatologic descriptions were not available in the remaining relevant articles.

Diagnosis of SOT GVHD

When GVHD was suspected, skin biopsies, chimerism studies and FISH were performed in almost all cases reported in the literature. Skin biopsies were helpful in confirming the clinical suspicion of SOT GVHD, as they often revealed vacuolar degeneration, necrotic keratinocytes, and satellite cell necrosis, microscopic features that are characteristic in skin biopsies of patients with hematopoietic cell transplantation-related GVHD. In one instance, when biopsy of the bone marrow failed to show chimerism, skin biopsy results were used to confirm the diagnosis of SOT GVHD⁵. Moreover, in a case report by Meves et al., FISH performed on skin biopsy specimens helped confirm the diagnosis of GVHD in sex-mismatched patients⁶³. In cases in which a PCR-based chimerism assay failed to reveal donor DNA in peripheral blood, FISH performed on skin biopsy specimens revealed a significant number of donor lymphocytes that helped solidify the diagnosis. HLA typing was performed in peripheral blood lymphocytes in 6 cases^{9,42,43,55,60,66}. In one study, donor lymphocytes were marked by immunohistochemical methods on skin biopsy specimens as well⁵⁶. HLA typing was performed by serologic techniques to test for specific donor HLA antigens in 3 cases^{29,51,56}. For instance, in a study conducted by Smith et al., when GVHD was suspected, the patient was re-typed for HLA-A and HLA-B antigens, which demonstrated a mixture of the patient and donor HLA types with a stronger reaction being the donor's HLA type⁵¹. HLA typing was particularly helpful in detecting the donor HLA phenotype when skin biopsy showed no signs of GVHD⁶⁵.

Complications of SOT GVHD

The triad of fever, diarrhea, and pancytopenia was documented in 11 of 115 (9.6%) patients who went on to be diagnosed with SOT GVHD. Sepsis and multi-organ failure were the two most common causes of death. For the 97 patients for whom clinical outcome could be discerned from the literature, 70 (72.2%) died. Of the 23 patients for whom the time interval between transplantation and death was reported, the time after transplant to death was on average 99.2 days. Of these patients, the average time to death from the appearance of a rash was 51.7 days.

DISCUSSION

Graft-versus-host disease is a potentially lethal complication of solid organ transplantation. While several case reports and series have been published previously, we are not aware of a systematic review of the literature on SOT GVHD, particularly with regards to the dermatologic manifestations. Based on our findings, we can conclude that the dermatologic

manifestations of SOT GVHD can develop within a few days to several months after transplant. The dermatologic presentation can also be varied, although it does seem to share clinical and microscopic features with hematopoietic cell transplantation-associated GVHD. Reported cases were associated with a high mortality rate.

Importantly, this literature review indicates that the dermatologic manifestations of SOT GVHD can be non-specific. Thus, particularly given the seriousness of the disease, it is essential that the consulting dermatologist have a high index of suspicion for this rare diagnosis and pursue confirmatory tests, such as a skin biopsy or other ancillary tests.

Our study demonstrates the importance of combining clinical and laboratory variables in predicting the likelihood of this disease. For instance, evidence of bone marrow or gastrointestinal tract involvement accompanying the development of a new skin eruption in the post-transplantation period may be suggestive of SOT GVHD. Though the triad of fever, diarrhea and pancytopenia was relatively infrequently observed in this population, this constellation of findings may be specific for SOT GVHD. Further studies are required to determine the specificity of these clinical features.

Currently available tests to confirm the diagnosis of SOT GVHD are not entirely sensitive. In the setting of hematopoietic cell transplantation, peripheral blood chimerism assays with only 5% sensitivity are required detect recipient bone marrow cells or graft failures. However, this sensitivity is inadequate to sufficiently exclude chimerism with a negative test in the setting of suspected SOT GVHD. While FISH can be helpful, its use is limited by the fact that it can only be applied when patients receive a transplant from a patient of the opposite sex.. We encourage future efforts to develop a more sensitive assay for chimerism in the setting of SOT GVHD.

Limitations to this systematic review include incomplete or general dermatologic descriptions in reported cases, as well as potential publication bias favoring the most fulminant and/or fatal cases.

CONCLUSION

SOT GVHD is a potentially fatal complication of solid organ transplantation that often presents with a non-specific skin eruption. Early recognition of this entity by the dermatologist, with supportive evidence from skin biopsy and possibly other ancillary tests, such as FISH or PCR-based chimerism studies, may decrease delay in diagnosis and allow for prompt initiation of appropriate treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CAPSULE SUMMARY

- Dermatologic manifestations of graft-versus-host disease after solid organ transplantation (SOT GVHD) are not well-known.
- Skin eruption appears early on and has varied clinical presentations.
- In patients who develop dermatologic signs following solid-organ transplantation, we advise dermatologists to have a high index of suspicion for this rare but potentially fatal entity.

Table 1.

Summary of data from systematic literature review

Total number of studies	61
Total number of cases	115
Organs transplanted	126
Liver	81/126(64.3%)
Pancreas	13/126(10.3%)
Lung	8/126 (6.3%)
Kidney	13/126(10.3%)
Heart	5/126 (3.9%)
Intestinal	6/126 (4.8%)
Dermatologic manifestations	101/115 = 87.8%
Average POD of appearance of skin manifestations	48.3 n=92 (range: 3–243)
Pruritic	5/101 (4.9%)
Morbilliform	2/101 (1.9%)
Confluent	6/101 (5.9%)
Desquamation	4/101 (3.9%)
Complications of SOT GVHD	
Total number of patients who died	70/97(72.2%)
Total number of patients who recovered	27/97 (27.8%)
Average POD of death	99.2 n=23
Common causes of death	
Infection	10
Hemorrhage	5
Sepsis	28
Multi-organ failure	14
Acute respiratory distress	2

*POD = Post-operative day