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

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Background: Graft-versus-host-disease (GVHD) after solid organ transplantation (SOT) is extremely rare.

Objective: To investigate the dermatologic manifestations and clinical outcomes of SOT GVHD.

Methods: Systematic literature review of SOT GVHD.

Results: After full-text article review, we included 61 articles, representing 115 patients and 126 transplanted organs. The most commonly transplanted organ was the liver (n = 81). Among 115 patients, 101 (87.8%) developed skin involvement. The eruption appeared an average of 48.3 days (range, 3-243 days) posttransplant and was pruritic in 5 of 101 (4.9%) cases. The eruption was described as morbilliform in 2 patients (1.9%), confluent in 6 (5.9%), and desquamative in 4 (3.9%) cases. In many cases, specific dermatologic descriptions were lacking. The mortality rate was 72.2%. Relative time of death was reported in 23 patients who died during the follow-up period. These patients died an average of 99.2 days (range, 22-270 days) posttransplant, or 50.9 days after the appearance of dermatologic symptoms. Frequent causes of death were sepsis and multiorgan failure.

Limitations: Incomplete descriptions of skin findings and potential publication bias resulting in publication of only the most severe cases.

Conclusions: GVHD is a potentially fatal condition that can occur after SOT and often presents with a skin rash. We recommend that dermatologists have a low threshold to consider and pursue this diagnosis in the setting of post-SOT skin eruption. (J Am Acad Dermatol 2018;78:1097-101.)

Key words: dermatopathology; graft-versus-host disease; transplant.

INTRODUCTION

Graft-versus-host-disease (GVHD) is a multisystem disease that can occur after blood and marrow or solid organ transplantation (SOT). 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 after SOT may present in 1 of 2 forms.[1] 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, or bone marrow.[1] Known risk factors for developing SOT GVHD include: African American race, human leukocyte antigen (HLA) mismatch, and cytomegalovirus infection,[2] as well as an underlying tumor diagnosis or neoadjuvant chemotherapy administered before the transplant.[3] While 3 case reports from the literature have shown that aggressive immunosuppression and plasmapheresis can be successful in treating SOT GVHD, there still exist challenges to treatment.[4-6]

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Patients with SOT GVHD may experience cutaneous involvement, but it has been our experience that the associated eruption is nonspecific 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 conducted a systematic review of available the relevant literature to better understand this rare but potentially serious complication of SOT, with an emphasis on its dermatologic manifestations.

CAPSULE SUMMARY

- Dermatologic manifestations of graft-versus-host disease after solid organ transplantation are not well-known.
- The skin eruption appears early in the course and has varied clinical presentations.
- In patients who develop skin changes after solid organ transplantation, dermatologists should have a high index of suspicion for this rare but potentially fatal entity.

METHODS

Literature search

With the assistance of a Masters level medical librarian (AF), 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 GVHD after SOT. Pediatric SOT GVHD cases were excluded. Becase of 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 specimen results, organ involvement and complications, treatment regimen, and 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 flow diagram is presented in Supplemental 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, because some patients received multiple organs.[4-64] SOT GVHD was most common after liver transplantation (n = 81, 64.3%). A summary of data from the existing literature can be found in Table I.

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 days[47,59]) 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%)[13,17,26,43,45,56] and 4 (3.9%)[26,49,50,62] patients, respectively. In 1 patient, the dermatologic symptoms initially began as a maculopapular eruption that progressed to one resembling toxic epidermal necrolysis.[59] 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 biopsy specimens were obtained, chimerism studies were conducted, and fluorescence in situ hybridization (FISH) was performed in almost all cases reported in the literature. Skin biopsy specimens were helpful in confirming the clinical suspicion of SOT GVHD because they often revealed vacuolar degeneration, necrotic keratinocytes, and satellite cell necrosis, microscopic features that are characteristic in skin biopsy specimens of patients with hematopoietic cell transplantation–related GVHD. In one instance, when a biopsy specimen of the bone marrow failed to reveal chimerism, the skin biopsy results were used to confirm the diagnosis of SOT GVHD.[5] Moreover, in a case report by Meves et al,[62] FISH