Late Appearance of Acute Graft-vs-Host Disease After Suspending or Tapering Immunosuppressive Drugs

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Background: Graft-vs-host disease (GVHD) is divided into acute and chronic phases based on time and clinical and histological features. The criterion of 100 days after transplantation for separating acute GVHD from chronic GVHD has been challenged on the following points: (1) the lichenoid rash of chronic GVHD may be observed as early as day 31 and acute GVHD may persist after day 100 in some cases, and (2) specific histological features do not consistently separate acute from chronic GVHD defined as the number of days after transplantation. However, the appearance of acute cutaneous GVHD after day 100 is not well established.

Observations: Three patients developed a rash with clinical and histological features of acute GVHD between days 153 and 192 after allogeneic bone marrow transplantation or peripheral blood stem cell transplantation. In all patients, the late flare of acute GVHD occurred after tapering or suspending the immunosuppressive regimen with cyclosporine or corticosteroids, and was accompanied by stigmata of chronic GVHD in other target organs.

Conclusions: The rash of acute GVHD may be observed as late as 192 days after transplantation, especially after tapering or suspending the immunosuppressive drugs, and should be considered in the differential diagnosis of late erythematous eruptions after transplantation.

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The constant increase in transplantation procedures over the last few years has made the follow-up of patients receiving grafts a widespread practice for many dermatologists. Graft-vs-host disease (GVHD) is the major cause of morbidity and mortality after bone marrow transplantation (BMT).

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Prophylactic administration of cyclosporine in combination with methotrexate or corticosteroids has been shown to produce a clinically important reduction in acute GVHD without changing the incidence of chronic GVHD. The role of tapering or suspending immunosuppressive drugs in the development of GVHD has not been completely resolved. The success of cyclosporine therapy in preventing acute GVHD was related to the patient's cyclosporine level in one study, but was not confirmed in a follow-up study. However, the study by Nash et al did find a relationship between the onset of acute GVHD and previous dose reductions of the combined therapy of cyclosporine and methotrexate.

Graft-vs-host disease has traditionally been divided into acute and chronic phases based on time course and clinical and histological features. The initial criterion of 100 days after transplantation for separating acute from chronic GVHD has been challenged because the lichenoid rash of chronic GVHD may be observed as early as day 31 after transplantation, and acute GVHD may persist after day 100 in some cases. In addition, a recent study indicates that specific histological features do not consistently separate acute from chronic GVHD as defined by days after BMT. However, the concept of acute cutaneous GVHD appearing after day 100 is not well established.

We describe 3 patients in whom a rash with clinical and histological features of acute GVHD developed, between days 153 and 192 after allogeneic BMT or peripheral blood stem cell transplantation.

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tion (PBSCT). In all patients, the late flare of acute GVHD occurred after tapering or suspending the immunosuppressive regimen (a combination of cyclosporine or corticosteroids) and was accompanied by the stigmata of chronic GVHD in other target organs.

REPORT OF CASES

CASE 1

A 27-year-old woman with chronic myelogenous leukemia underwent an allogeneic PBSCT from her sister after preparation with cyclophosphamide therapy and total body irradiation. She received GVHD prophylaxis of cyclosporine from pre-PBSCT day 1 on, and intravenous methotrexate infusion on post-PBSCT days 1, 3, 6, and 11.

Between post-PBSCT days 17 and 21, she developed acute cutaneous GVHD grade 2, and acute hepatic GVHD grade 3, which resolved after a short course of methylprednisolone sodium succinate. On post-PBSCT day 34, prophylaxis for Pneumocystis carinii with a combination of sulfamethoxazole-trimethoprim was begun. The daily dosage of cyclosporine was tapered gradually from post-PBSCT day 59 (6.8 mg/kg of body weight), and was reduced more drastically on day 167 (1.4 to 0.7 mg/kg of body weight daily). The concentration of cyclosporine in the patient’s serum dropped accordingly from 72 ng/mL on day 157 to 44 ng/mL on day 168 and to 16 ng/mL on day 180. On post-PBSCT day 181, a pruritic erythematous macular eruption developed on the anterior thorax, back (Figure 1), arms, and thighs. The rash became more intense over the next few days and extended to the patient’s forearms, calves, and the dorsal surface of both hands and feet, involving more than 50% of the skin surface. Physical examination also revealed reticulate white lesions on the right buccal mucosa. A skin biopsy specimen showed basal vacuolization of the dermoepidermal junction, scattered necrotic keratinocytes, moderate spongiosis with occasional vesicle formation, and exocytosis of lymphocytes. The underlying papillary dermis showed a sparse perivascular predominantly lymphocytic infiltrate with occasional eosinophils. The findings were interpreted as a possible drug reaction vs acute GVHD grade 2. A biopsy specimen obtained from the buccal mucosa was consistent with lichenoid GVHD grade 2.

On post-PBSCT day 187, the daily dose of cyclosporine was increased to 2 mg/kg of body weight. During the next few days the rash became more intense and extended to the patient’s neck and cheeks, and new lesions appeared on the dorsal surface of both hands and feet, involving 80% of the skin surface. On post-PBSCT day 192, treatment was started with prednisone at a daily dose of 1.7 mg/kg of body weight. A second biopsy specimen showed intense basal vacuolization of the dermoepidermal junction, numerous necrotic keratinocytes, and a perivascular lymphocytic infiltrate in the papillary dermis (Figure 2). The findings were consistent with acute GVHD grade 2.

The treatment with systemic corticosteroids stopped the spread of the cutaneous lesions, which had become confluent (Figure 3), and a gradual diminution of the erythema with subsequent appearance of postinflammatory hyperpigmentation was seen over the next few days. Lichenoid lesions on the skin have not been observed at any moment during the course of treatment. She also did not develop signs or symptoms consistent with intestinal or hepatic GVHD. On post-PBSCT day 226, additional erythematous macular le-
sions appeared on the patient’s face, which extended during the next 48 hours. On post-PBSCT day 228, treatment with sulfamethoxazole-trimethoprim was discontinued. The lesions resolved without additional treatment or change in the dosage of the systemic corticosteroids. However, sulfamethoxazole-trimethoprim therapy was reintroduced on post-PBSCT day 243 without complications.

CASE 2

A 34-year-old woman who had refractory anemia with an excess of blasts underwent allogeneic BMT from an unrelated donor after preparation with cyclophosphamide therapy and total body irradiation. She received GVHD prophylaxis with cyclosporine from pre-BMT day 1 until post-BMT day 160, and intravenous methotrexate therapy on post-BMT days 1, 3, 6, and 11.

Between post-BMT days 17 and 19, she developed acute cutaneous GVHD grade 3, intestinal GVHD grade 2, all of which resolved after treatment with methylprednisolone. The systemic corticosteroid doses were gradually tapered and suspended on post-BMT day 63. Prophylaxis for P carinii with a combination of sulfamethoxazole-trimethoprim was started on post-BMT day 56. The daily dosage of cyclosporine was gradually tapered from 5.6 mg/kg of body weight on day 78 to 4 mg/kg of body weight on day 155, was reduced rapidly over the next week, and was discontinued on day 160.

On post-BMT day 192, an erythematous macular eruption developed on the patient’s face, neck, trunk, and arms with involvement of the palms. The rash became more intense and confluent over the next few days involving more than 50% of the skin surface. Physical examination also revealed several reticulate white lesions on the buccal mucosa. A skin biopsy specimen obtained on post-BMT day 197 showed intense basal vacuolization of the dermoepidermal junction, numerous necrotic keratinocytes, and a discrete perivascular predominantly lymphocytic infiltrate with occasional eosinophils in the papillary dermis. These findings were interpreted as acute cutaneous GVHD grade 2.

On post-BMT day 197, treatment was started with prednisone at a daily dose of 1.7 mg/kg of body weight, which resolved the rash. Lichenoid GVHD lesions on the skin have not been observed at any time during the course of treatment. However, the lesions on the buccal mucosa were recalcitrant; she has never been free of lesions. A biopsy specimen obtained from the buccal mucosa (on post-BMT day 216) was consistent with GVHD grade 2. On post-BMT day 209, she developed a bilateral keratoconjunctivitis with positive Schirmer test. She did not develop signs or symptoms consistent with gastrointestinal or hepatic GVHD.

CASE 3

A 21-year-old woman with acute lymphoblastic leukemia underwent an HLA-identical allogeneic BMT from her sister following a preparation with a regimen of cyclophosphamide therapy and total body irradiation. She received GVHD prophylaxis with cyclosporine from pre-BMT day 1 until post-BMT day 60, when the drug treatment was discontinued because of renal failure.

Between post-BMT days 17 and 21, she developed acute cutaneous GVHD grade 3 and intestinal GVHD grade 4, which resolved with methylprednisolone therapy. The treatment with systemic corticosteroids was discontinued on post-BMT day 38 but was reintroduced on day 39 because of a new flare of intestinal GVHD that ceased in 24 hours. Between post-BMT days 39 and 54, she also developed hepatic GVHD grade 1. Although the levels of bilirubin normalized on post-BMT day 59, other liver values remained abnormal.

She received prophylaxis for P carinii with sulfamethoxazole-trimethoprim from post-BMT day 62 on. On day 89, she developed bilateral keratoconjunctivitis with a positive Schirmer test. The daily dose of methylprednisolone sodium succinate was gradually tapered from 1 mg/kg of body weight on day 88 to 0.5 mg/kg of body weight on day 144. On day 151, the daily dosage was rapidly reduced to 0.3 mg/kg of body weight every other day.

On post-BMT day 153, a pruritic erythematous tenuous macular eruption developed on the patient’s forearms, wrists, and thighs. The rash became more intense over the next few days and became generalized with involvement of the patient’s cheeks, pinnae, retroauricular areas, neck, trunk, arms, thighs, and the dorsal surface of both hands with involvement of the palms. The rash affected 50% to 80% of the skin surface. No lesions were observed on the oral mucosa. A biopsy specimen obtained from the abdomen on post-BMT day 164 was consistent with GVHD grade 2.

On post-BMT day 167, the daily dosage of methylprednisolone sodium succinate was increased to 1 mg/kg of body weight every other day, which resolved the rash. Lichenoid lesions have not been observed on the skin, but a physical examination on post-BMT day 218 revealed lichenoid lesions in oral mucosa. She did not develop signs or symptoms consistent with gastrointestinal GVHD. However, she developed hepatic GVHD grade 4 and on post-BMT day 240, she died of hepatic failure. An autopsy liver sample confirmed the diagnosis of chronic hepatic GVHD. On post-BMT day 153, treatment with sulfamethoxazole-trimethoprim had been discontinued because of the rash but was reintroduced on day 181 without any cutaneous complications.

Graft-vs-host disease is still divided into acute and chronic forms defined as number of days after transplantation. Acute cutaneous GVHD usually presents as a pruritic erythematous, macular rash around the time of marrow engraftment, generally between post-BMT days 10 and 40.10,13 Chronic cutaneous GVHD presents as lichenoid skin and/or oral mucous membrane lesions, and/or as sclerodermoid skin lesions with poikiloderma and sclerosis, all of which appear usually more than 100 days after BMT.10,12,13 The histological features of acute and chronic GVHD both include a vacuolar in-
terface dermatitis with a dermal infiltrate of lymphocytes, basal vacuolar alteration, and necrosis of epidermal cells.\textsuperscript{11, 14} Whereas the added findings of acanthosis, hypergranulosus, hyperkeratosis, and saw-toothed rete ridges are considered diagnostic characteristics of chronic lichenoid GVHD\textsuperscript{9, 15} the sclerodermoid form is characterized by sclerosis of the dermis with progressive entrapment and destruction of adnexal structures and less prominent interface dermatitis.\textsuperscript{12, 16}

Despite the apparent simplicity of the traditional classification of GVHD into acute and chronic phases defined as number of days after transplantation, this separation is not that precise. The initial criterion of 100 days after transplantation for separation into acute and chronic GVHD has been challenged because the lichenoid rash of chronic GVHD may be observed as early as day 31 after transplantation\textsuperscript{7} and acute GVHD may persist after day 100 in some cases.\textsuperscript{6} Moreover, a recent study showed that fully evolved histological features of chronic lichenoid GVHD and acute GVHD do not consistently reflect the clinical phase as defined by number of days after BMT.\textsuperscript{9} In addition, atypical variants of cutaneous GVHD have been described that do not fit into this diagnostic classification either. Hyperacute or explosive presentations of GVHD may be observed after allogeneic transplantations without or with insufficient GVHD prophylaxis, which are characterized by severe systemic involvement, high mortality, and an erythroderma that evolves from acute to lichenoid within several days of onset with histological features of both acute and chronic lichenoid GVHD.\textsuperscript{11, 17, 18}

Although the criterion of 100 days for separating acute from chronic GVHD has been challenged, the concept of acute cutaneous GVHD appearing after day 100 (without progression to lichenoid or sclerodermoid GVHD) is not well established. To our surprise, we found only 2 references in the hematologic literature dealing with this form. One reference mentions the appearance of acute GVHD several months after BMT on withdrawal of cyclosporine therapy in some patients, but it does not describe the clinical and histological features of these patients.\textsuperscript{19} A case report described a patient in whom a clinical syndrome suggestive of acute GVHD developed 236 days after BMT and several weeks after remission induction with high-dose intravenous cytarabine.\textsuperscript{20}

We describe 3 patients in whom a rash with clinical and histological features of acute GVHD developed between days 153 and 192 after allogeneic BMT or allogeneic PBSCT. In all patients, the rash constituted a recurrence of acute GVHD, which was accompanied by stigmata of chronic GVHD in other target organs and occurred after tapering or suspending the immunosuppressive regimen of the combination of cyclosporine and corticosteroids. The rashes resolved with treatment with cyclosporine and/or corticosteroids without progression to lichenoid or sclerodermatous GVHD. The existence of late acute cutaneous GVHD complicates the differential diagnosis of late erythematous eruptions after transplantation, which includes chronic lichenoid GVHD, drug hypersensitivity eruptions, sepsis, and viral exanthems as principal alternative options. However, none of these options were likely in our patients.

Our patients had stigmata of chronic GVHD in other target organs, but the clinical and histological features of the rash were inconsistent with lichenoid or sclerodermoid GVHD at any time. All 3 patients were receiving prophylactic treatment with a combination of sulfamethoxazole-trimethoprim and folic acid at the onset of rash. However, these drugs did not cause the eruption as the rash resolved despite the maintenance of treatment or their later reintroduction without producing a rash.

The histological findings of a viral exanthem may be rather nonspecific. There was no serologic or culture evidence of sepsis or infection with herpesvirus or cytomegalovirus in any of the patients at the onset of the rash, and none of the biopsy specimens showed the typical cytopathic changes of these 2 viruses.

There seemed to be a relationship between the appearance of the rash and previous dose reductions of the GVHD immunosuppressive regimen in patients 1 and 3. The rash appeared 14 days after a 50% dose reduction in cyclosporine in patient 1, and during this period the serum levels of cyclosporine had dropped 67%. In patient 3, the rash developed 9 days after a 67% dose reduction in methylprednisolone. However, the relationship was less clear in patient 2, as the rash appeared 32 days after suspending cyclosporine therapy. The role of the tapering or suspending of the immunosuppressive drugs in the development of GVHD has not been completely resolved. One study found a significant correlation between the serum cyclosporine concentration for a given week and the risk that acute GVHD would develop during the next week.\textsuperscript{3} However, a follow-up study could not confirm this correlation but did find a relationship between the appearance of acute GVHD and previous dose reductions of methotrexate and cyclosporine therapy.\textsuperscript{6}

Although the prophylactic administration of cyclosporine combined with methotrexate or corticosteroids has been shown to be beneficial in the prevention of acute GVHD, it has not changed the incidence of chronic GVHD.\textsuperscript{1, 4, 21} In our patients, the acute rash appeared after tapering or withdrawal of the immunosuppressive regimen with cyclosporine or corticosteroids. Reticulate white lesions of the buccal mucosae also developed when cyclosporine therapy was tapered or withdrawn in patients 1 and 2. However, bilateral keratoconjunctivitis with a positive Schirmer test and chronic hepatic GVHD developed despite the treatment with methylprednisolone in patient 3. In conclusion, the rash of acute GVHD may be observed as late as 192 days after transplantation, especially after tapering or suspending immunosuppressive drugs, and should be considered in the differential diagnosis of late erythematosus eruptions after transplantation. The time of occurrence is the only reliable parameter for the clinical picture of GVHD, and there may exist overlap cases between acute and chronic lichenoid GVHD.

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