Induction of Hyperacute Graft-vs-Host Disease After Donor Leukocyte Infusions

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Background: Infusions of leukocytes obtained from the original bone marrow donor is a new approach for treating patients who have a relapse of leukemia after allogeneic bone marrow transplantation. Up to 90% of patients who achieved remission developed graft-vs-host disease (GVHD). However, any description of the clinical and histologic features in these cases is lacking.

Observations: We describe 2 patients in whom a severe, peculiar, hyperacute, fatal GVHD developed after treatment with donor leukocyte infusions and interferon alfa. The patients had not received any additional chemotherapy or GVHD prophylaxis. In both patients, the eruption started with the appearance of erythematous plaques at the interferon alfa injection sites, and a generalized maculopapular eruption subsequently developed. The clinical lesions evolved from acute to lichenoid within several days. The histologic examination also demonstrated unusual findings and showed features of both acute and chronic lichenoid GVHD.

Conclusions: Donor leukocyte infusions without GVHD prophylaxis may provoke a severe fatal hyperacute GVHD. In the cases presented herein, we discuss the significance of the rapid clinical evolution from acute to lichenoid and the combination of histologic features of both acute and chronic GVHD in the biopsy specimens.

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During the past 25 years, more than 60,000 patients have undergone allogeneic bone marrow transplantation (BMT) worldwide. Acute graft-vs-host disease (GVHD) is still the main complication of allogeneic BMT and is responsible for the relatively high mortality and morbidity rates in these patients. Acute GVHD may also rarely occur after autologous and syngeneic BMT, solid-organ transplantation, and transfusions.1

Infusions of leukocytes obtained from the original bone marrow donor represent a new approach for treating patients who have a relapse of leukemia after allogeneic BMT, which intends to obtain a graft-vs-leukemia effect from the T cells of the donor.2 7 This therapy avoids the high mortality rate of a second BMT and induces complete remission in up to 73% of patients with chronic myeloid leukemia (CML) and in 29% of patients with acute myeloid leukemia or myelodysplastic syndrome.5 7 However, these donor leukocyte infusions (DLIs) have been associated with GVHD in up to 90% of patients who achieved remission.8 The reports of GVHD in these patients have only appeared in the hematologic literature, and any description of the clinical and histologic features is lacking.

We describe herein 2 patients with acute lymphoblastic leukemia (ALL) and CML, respectively, both of whom had a relapse after undergoing allogeneic BMT and in whom a severe peculiar hyperacute GVHD developed after treatment with interferon alfa and one or more DLIs. The patients did not receive any additional chemotherapy or GVHD prophylaxis. A complete clinical and histologic evaluation was performed in both patients.

REPORT OF CASES

CASE 1

A 30-year-old man suffered a relapse of his Philadelphia chromosome–positive ALL after receiving an allogeneic BMT from an HLA-identical sibling donor. Treatment was started with subcutaneous interferon alfa, and the patient received a single donor lymphocyte infusion at a total dose of $1 \times 10^7$ lymphocytes per kilogram of recipient weight. The donor leukocytes had been obtained from the donor by basal leukapheresis without any previous stimulation. The patient did not receive any GVHD prophylaxis.
Nine days after the infusion, erythematous plaques appeared on the lateral aspect of both arms at the interferon alfa injection sites (Figure 1). Between 3 and 4 days later, an asymptomatic erythematous maculopapular rash developed over the face, trunk, buttocks, arms, and thighs, with involvement of the axillae, groins, and palms. The erythematous macular and papular lesions, which were discrete and well defined, became confluent in the following days and evolved into an erythroderma. There was also an intense involvement of the oral mucosa with erythema, erosions, and several white plaques.

Three biopsy specimens were obtained and showed basal vacuolization with occasional satellitosis and numerous necrotic keratinocytes, which were predominantly seen in the basal layer but also at higher levels of the epidermis (Figure 2). Similar findings were observed in the basal layer of the follicular epithelium. In 2 of the 3 biopsy specimens, these epidermal changes were associated with compact orthokeratotic and parakersatotic hyperkeratosis, hypergranulosis, acanthosis, saw-toothed rete ridges (Figure 3), and an intensely abnormal maturation of the lower part of the epidermis that consisted of large keratinocytes with irregular large nuclei, prominent nucleoli, and frequent mitotic figures. Cytologic atypia was also observed in the straight duct of the eccrine glands. The underlying papillary dermis showed a light perivascular lymphocytic infiltrate and occasional melanophages and eosinophils in all biopsy specimens. Immunohistochemical study revealed increased CD1+ and keratinocyte intercellular adhesion molecule 1 (ICAM-1) in the basal and suprabasal layers of the epidermis. The dermal infiltrate was composed of a similar amount of CD4+ cells and CD8+ cells, but there were no natural killer cells.

One day after the onset of the rash, treatment was started with methylprednisolone sodium succinate, which stopped the spread of the cutaneous lesions, but did not improve them. Instead, the lesions became violaceous, like those of lichen planus. Between days 14 and 16 after the DLI, the patient also developed severe intestinal and hepatic GVHD, which resulted in his death 66 days later, even though both hematologic and cytogenetic remission had been achieved.
CASE 2

A 36-year-old woman with CML received treatment with subcutaneous injections of interferon alfa, because of a cytogenetic relapse after receiving a 1-antigen HLA-A mismatched BMT from a brother. After 6 months of treatment, no cytogenetic response was observed, and the patient was included in the treatment program of DLI, while continuing the interferon alfa treatment. The donor leukocytes were infused in aliquoted doses of 5 to $10 \times 10^7$ leukocytes per kilogram of recipient weight. A total of $5 \times 10^8$ donor leukocytes per kilogram and $3.14 \times 10^8$ CD3+ cells per kilogram were infused. The patient did not receive any GVHD prophylaxis.

Fifty-seven days after the first infusion and 11 days after the last infusion of lymphocytes, erythematous plaques appeared on both arms at the interferon alfa injection sites. Between 24 and 48 hours later, the patient developed an erythematous maculopapular rash predominantly involving the face, trunk, arms, thighs, palms, soles, and periangual areas. She also developed a high fever and severe bilateral keratitis, which resulted in blindness of both eyes. The rash became more intense over the following days, with confluence of the lesions and progression to edema and vesicles but without detachment of the epidermis. Some of the lesions adopted an erythema multiforme–like pattern (Figure 4). A biopsy specimen was obtained and showed intense basal vacuolization with occasional satellitosis and numerous necrotic keratinocytes in the epidermis as well as the follicular epithelium. These changes resulted in extensive separation of the dermo-

epidermal junction (Figure 5). The underlying papillary dermis showed occasional melanophages and a superficial perivascular infiltrate that was predominantly lymphocytic with moderate eosinophilia. On day 15 after DLI, treatment was started with methylprednisolone, without improvement of the cutaneous eruption, the lesions of which became violaceous, similar to those in case 1 (Figure 6). A second biopsy specimen showed findings similar to those described in case 1, but they lacked the dysmaturative changes of the epidermis. Immunohistochemical study showed little expression of CD1+ and almost no expression of ICAM-1. The dermal infiltrate was light but was otherwise similar in composition to that in case 1.

On day 17 after DLI, the patient also developed intestinal GVHD and severe hepatic GVHD, which resulted in her death 71 days later. Neither hematologic nor cytogenetic remission had been achieved.

COMMENT

The administration of DLIs has been reported to result in hematologic and cytogenetic remissions in many patients who have a relapse of CML after BMT. However, up to 90% of the patients who achieved remission developed GVHD. Studies in rodent models and subsequent clinical experience in humans have shown that immunocompetent donor cells contribute to the an-
tile leukemias. This immunological response is often referred to as a graft-vs-leukemia effect. Although the toxic effects of adoptive immunotherapy were minimal in the initial report, other preliminary studies have documented severe GVHD and bone marrow aplasia in some patients. We describe 2 patients in whom a hyperacute GVHD, grade IV, developed after adoptive immunotherapy, which consisted of stage 3 or 4 cutaneous GVHD, stage 2 or 3 enteric disease, and stage 4 hepatic disease. The treatment failed and both patients died. In both patients, the eruption started in a peculiar way, with development of erythematous plaques at the interferon alfa injection sites. Immediately thereafter, the patients developed a generalized erythematous asymptomatic rash that was more pronounced in proximal areas. Patient 1 also had intense involvement of the oral mucosa, with erosions and lichenoid plaques, whereas patient 2 developed severe bilateral keratitis, which resulted in blindness of both eyes. The latter patient also exhibited erythema multiforme-like lesions and intense erythema and edema of the periangual areas of the hands and feet. The rapid evolution of the cutaneous lesions from acute to lichenoid in both cases was striking.

The histologic examination also demonstrated unusual findings and showed features of both acute and chronic lichenoid GVHD. In addition to the basal vacuolization, spongiosis, and necrotic keratinocytes, the epidermis showed orthokeratotic and parakeratotic hyperkeratosis, hypergranulosis, acanthosis, and saw-toothed rete ridges, which have traditionally been considered diagnostic characteristics of chronic lichenoid disease, although a bandlike upper dermal infiltrate was lacking in all biopsy specimens. The histologic examination also showed a perivascular upper dermal lymphocytic infiltrate in all biopsy specimens, which is considered an additional criterion of acute GVHD. There was also intense involvement of the follicular epithelium with basal vacuolization, spongiosis, and necrotic keratinocytes. The cytotoxic folliculitis is considered virtually omnipresent in GVHD, with the parafollicular bulge as the early and preferential target. Another conspicuous finding in our cases was the high number of necrotic keratinocytes, which were associated with an intensely abnormal maturation of the lower part of the epidermis. Although GVHD has traditionally been divided into acute and chronic phases based on the time course and the clinical and histologic features, a recent study indicates that specific histologic parameters do not consistently separate acute from chronic GVHD. In that study, histologic features of chronic lichenoid GVHD were observed as early as 33 days after BMT and features of acute GVHD as late as 481 days after BMT. However, in our patient 1, clinically hyperacute GVHD with histologic features of chronic lichenoid GVHD developed as early as 17 days after the infusion of lymphocytes. We would like to emphasize the early appearance and severity of the GVHD in our patients, as well as the rapid clinical evolution from acute to lichenoid in several days.

The immunohistochemical study in case 1 showed features of the lichenoid phase of GVHD, with an increased number of Langerhans cells and a moderate expression of the keratinocytes for ICAM-1. However, little expression of CD1+ and almost no expression of ICAM-1 were found in case 2. Although natural killer cells have been implicated in the cytotoxic effects of GVHD, they were not observed in our cases.

Hyperacute GVHD was first described by Sullivan et al as a syndrome that consisted of stages 3-4 skin disease, which was present in all patients and was accompanied by high fever and intestinal and/or hepatic GVHD in most patients. The onset was between 7 and 29 days after BMT. Their patients had not received any postgrafting prophylaxis for GVHD. In our cases, the clinical findings were similar to those described by Sullivan and colleagues, but instead of BMT our patients received one or more DLI. Postgrafting prophylaxis for GVHD was not given either. Moreover, our patients did not receive any additional immunosuppressive therapy before DLI.

Although this practice is not standard at the present time, both patients received interferon alfa in addition to DLI, which could have contributed in part to the clinical behavior of the GVHD. Interferon alfa therapy probably acted as a stimulus in the afferent phase of the disease. The fact that the clinical eruption started with erythematous plaques at the interferon alfa injection sites supports this hypothesis. Recently, several cases have been described in which the use of subcutaneous injections of interferon and other cytokines was associated with the development of erythematous plaques at the injection sites, with progression to ulceration and necrosis. On the other hand, treatment with interferon enhances the expression of HLA class II molecules on the surface of different cells, which could increase the possibility of GVHD. The donor T-cell lymphocytes are essential for the engraftment and the GVHD are, at least in part, responsible for the graft-vs-leukemia effect, which improves the rate of remissions. The severity of GVHD has been correlated with the number of donor T cells. However, in both our patients, a severe GVHD developed with different numbers of donor T cells.

Although the benefits of treating a relapse of CML with transfusions of donor lymphocytes are evident, the genetic manipulation of donor lymphocytes may increase the efficacy and safety of this therapy and expand its application to a larger number of patients. The genetic manipulation could improve the control of GVHD without losing the beneficial graft-vs-leukemia effect.

Although GVHD has been reported as a complication of DLI in several hematologic journals, we could not find any description of this outcome in the dermatologic literature. We would like to alert dermatologists to the possibility of this result and to emphasize the peculiar clinical and histologic findings, as well as the fatal outcome of our patients.

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REFERENCES