**Eczematoid Graft-vs-Host Disease**

*A Novel Form of Chronic Cutaneous Graft-vs-Host Disease and Its Response to Psoralen–UV-A Therapy*

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**Background:** Chronic cutaneous graft-vs-host disease (GVHD) is generally classified by whether lesions have a lichenoid or sclerodermatous morphology. Other unusual clinical forms have been reported that exhibit the features of dermatomyositis and lupus erythematosus. Within a large population of individuals who underwent allogeneic stem cell transplantation because of hematologic malignancy, a group of patients was identified in whom severe and persistent eczema developed.

**Observations:** We prospectively evaluated 10 adult patients with unexplained eczematous dermatosis after allogeneic hematopoietic stem cell transplantation. The dermatosis developed between 2 and 18 months (mean, 7.5 months) after receipt of the transplant, exhibited the typical clinical features of dermatitis, and became erythrodermic in each case. The patient group had strong risk factors for chronic cutaneous GVHD: 8 had received a transplant from an unrelated donor, 7 had evidence of extracutaneous GVHD, and 7 had a history of acute cutaneous GVHD. Sampling of lesional skin revealed the histologic features of GVHD coexisting with the changes of dermatitis. The patients were treated with topical corticosteroid and systemic immunosuppressive agents. Six patients also received psoralen–UV-A. Four patients achieved prolonged remission. Six patients died, 5 of infective complications and 1 of relapsed leukemia.

**Conclusions:** The eczematous dermatosis observed represents a novel form of chronic cutaneous GVHD that we named *eczematoid GVHD*. Eczematoid GVHD is an aggressive, chronic dermatosis that requires substantial immunosuppression therapy to achieve control. It is associated with a poor prognosis. Although atopy can be transmitted to an individual from a hematopoietic stem cell transplant, none of the donors in this series gave a history of an atopic disorder. Therefore, other factors must be implicated in provoking the expression of an eczematous phenotype in individuals with underlying chronic graft-vs-host activity.

*Arch Dermatol. 2007;143(9):1157-1162*
Rarely, GVHD variants occur that exhibit the features of autoimmune connective tissue diseases such as dermatomyositis and lupus erythematosus. Two reports cite eczematous GVHD. We studied patients who developed cutaneous GVHD after HSCT performed in the Department of Haematological Medicine at King's College Hospital, London, England. Patterns of GVHD manifestation, natural history, response to treatment, and outcome were recorded for all patients. Within this population, a distinct group has been identified characterized by persistent, widespread, chronic eczematous dermatosis occurring several months after allogeneic HSCT. The eruption demonstrates the histopathologic changes of both dermatitis and a GVH reaction, and we, therefore, suggest that it represents a manifestation of chronic cutaneous GVHD that warrants reporting and further investigation.

METHODS

PATIENTS

Between January 1, 2001, and December 31, 2004, 254 patients underwent allogeneic HSCT in the Department of Haematological Medicine at King's College Hospital. Of these patients, 10 were identified who developed chronic eczematous dermatosis after HSCT (eTable; available at: http://www.archdermatol.com). The group consisted of 8 men and 2 women, with a mean age at onset of dermatosis at 54.5 years (age range, 18-65 years). All patients had undergone allogeneic HSCT for the treatment of a hematologic malignancy (acute myeloid leukemia, 3 patients; chronic myeloid leukemia, 1; myelodysplastic syndrome, 2; chronic myelomonocytic leukemia, 2; myelodysplasia, 1; and acute lymphoblastic leukemia, 1). Dermatosis developed between 2 and 18 months (mean, 7.5 months) after HSCT. One patient had a history of atopic dermatitis, 2 had a history of asthma and hayfever, and 1 had a history of psoriasis. Drugs being taken by patients at the onset of dermatosis included prednisolone, cyclosporine, tacrolimus, phenoxymethyl-penicillin, fluconazole, amphotericin B, and acyclovir.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

All 10 patients received an allogeneic stem cell transplant. Stem cells were derived from the peripheral blood in 7 patients and bone marrow in 3. In 8 patients, the transplant was from a volunteer unrelated donor; in 2, the donor was a sibling (eTable). There was a donor-recipient sex mismatch in 3 of 10 transplantations and a donor-recipient cytomegalovirus mismatch in another 3 transplantations (eTable). None of the donors reported a history of atopy (atopic dermatitis, asthma, or eczema). One donor reported a history of mild psoriasis (the recipient was patient 5). The conditioning regimen, described previously, included alemtuzumab (Campath; Genzyme Corp, Cambridge, Massachusetts) in all patients but was otherwise.

Figure 1. Widespread, intensely pruritic, eczematous eruption in patient 7 (A) and patient 2 (B). During the course of the illness, all patients developed erythroderma with thermoregulatory dysfunction and dependent edema (B).
of reduced intensity in 9 patients (fludarabine phosphate, 150 mg/m²; busulfan, 8 mg/kg; and alemtuzumab, 100 mg) and of standard intensity in patient 7 (total body irradiation; cyclophosphamide; busulfan, 8 mg/kg; and alemtuzumab, 100 mg).

RISK FACTORS FOR GVHD

All 10 patients had received GVHD prophylaxis with cyclosporine and all transplants were T cell depleted in vivo using alemtuzumab in the conditioning regimen. Matching for donor relation, sex, and cytomegalovirus status is described above in “Hematopoietic Stem Cell Transplantation” subsection of the “Methods” section (eTable). Four patients had evidence of chronic hepatic, gastrointestinal GVHD, or both, occurring concurrently with the eczematous dermatosis. Seven patients were known to have had preceding acute cutaneous GVHD (eTable), and, in these patients, the eczematous dermatosis occurred 2 to 16 months (mean, 7.7 months) after acute GVHD. In 6 patients, the eruption appeared some months after acute GVHD (quiescent pattern), and in 1 patient (patient 3), it developed immediately after the acute episode (progressive pattern). Three patients (patients 4, 7, and 9) received donor lymphocyte infusions after HSCT (eTable). In these patients, the donor lymphocyte infusion was administered 13 weeks (patient 7) or 14 weeks (patients 4 and 9) after HSCT and 2 to 6 weeks before the onset of eczematous dermatosis. All patients received standard GVHD prophylaxis with cyclosporine and prednisolone in the first few months after HSCT. In 3 patients, the eczematous dermatosis developed as prophylactic immunosuppression therapy was being tapered in the 2 to 4 months after HSCT.

CLINICAL FEATURES

The eruption was similar in each patient and consisted of diffuse erythema and fine scaling, suggestive of eczema (Figure 1). Signs of impetiginization (colonization by Staphylococcus aureus) were frequently observed. Weeping in involved skin was common. Vesicles or pustules were not seen. Pruritus was usually severe and accompanied by excoriation. One patient had marked ichthyotic scaling, especially on the face and scalp (Figure 2). Palmoplantar hyperkeratosis was prominent in 7 of 10 patients (Figure 2). In all patients, the eczema rapidly became widespread, leading to erythroderma (exfoliative dermatitis). Erythrodermic involvement was complicated by thermoregulatory dysfunction, thirst, and dependent edema (Figure 1).

HISTOPATHOLOGIC FEATURES

Biopsy specimens were obtained from the affected skin in all patients. In each case, the histologic features of GVHD coexisted with the changes of dermatitis (Figure 3). The GVH reaction was indicated by satellite cell necrosis, and the presence of parakeratosis, lymphocyte exocytosis, and epidermal spongiosis reflected the clinical appearance of eczema (Figure 3). The dermal changes were less marked, often showing a sparse perivascular lymphocytic infiltrate. Eosinophils were admixed in the infiltrate in 4 patients. The combined features were not always present in the first biopsy specimen, and, in some patients, as many as 3 samples were necessary to indicate the eczematoid pattern of GVHD.

TREATMENT

First-line therapy for all patients was a regimen of an emollient, a potent topical corticosteroid ointment, and a sedating antihistamine taken at bedtime. Oral antibiotics were given when the dermatosis was complicated by secondary bacterial infection. Nine of 10 patients required hospital admission at least once during the course of their illness. Inpatient management
was considered necessary when systemic symptoms arising from the erythroderma (eg, thirst, shivering, or malaise) were prominent or if first-line therapy was ineffective in controlling the dermatosis. As well as delivering maximal topical therapy, erythroderma was treated with systemic immunosuppression with one or more of the following: psoralen–UV-A (PUVA), prednisolone, methylprednisolone, azathioprine, cyclosporine, tacrolimus, or mycophenolate mofetil (Table). In an attempt to limit systemic immunosuppression, 6 patients were treated with PUVA using oral psoralen (5-methoxypsoralen) and a UV-A dosimetry regimen similar to that used to treat atopic dermatitis (Table). Psoralen–UV-A was delivered twice weekly starting at a dose of 0.5 J/cm² and increasing the dose by 0.5 J/cm² increments at each treatment to a maximum dose of 5 J/cm². The duration of PUVA therapy was 12 to 20 weeks.

The course of dermatosis was prolonged in all 10 patients and did not tend to remit spontaneously. The shortest period of active involvement was 4 months, in 2 patients; both patients died with active eczematoid GVHD 4 months after the onset of dermatosis. The longest period of active involvement was 20 months (mean, 9.2 months; Table). The shortest follow-up was 4 months, and the longest was 42 months (mean, 15.5 months). Seven of the 10 patients also developed features of extracutaneous chronic GVHD, with hepatic involvement in 5 patients, bronchiolitis obliterans in 2, and involvement of the gastrointestinal tract in 2 (Table).

In 2 patients, the dermatosis was controlled with topical agents and systemic immunosuppressant agents (prednisolone and mycophenolate mofetil in patient 8 and prednisolone, tacrolimus, and mycophenolate mofetil in patient 10). Four of the 6 patients treated with PUVA responded successfully, achieving complete cutaneous clearance, and remission was maintained with only low-dose systemic immunosuppression therapy (eg, prednisolone, 1–5 mg/d) or no systemic immunosuppression therapy. In 2 of the patients who responded to PUVA (patients 2 and 6), treatment was hampered by the presence of secondary infection with methicillin-resistant S aureus, and the dermatosis resolved only after staphylococcal eradication.

Six patients died. The cause of death was considered to be bacterial sepsis in 2 patients, disseminated Aspergillus species infection in 2, and cryptococcosis in 1 (Table). 1 patient had a relapse of acute myelocytic leukemia. Two patients (patients 4 and 7) who died of septic complications had required prolonged exposure to high doses of systemic immunosuppressant agents to control the cutaneous GVHD. Secondary skin infection in patient 4 was probably the source of fatal overwhelming sepsis.

Four patients1,3,8,10 have achieved long-term remission (12–42 months; mean, 24 months) of the eczematoid GVHD; 2 (patients 1 and 5) received PUVA and 2 (patients 8 and 10) did not (Table). In these patients, the hematologic malignancy has also remained in remission.

We describe 10 patients in whom a widespread, chronic dermatitic eruption developed after allogeneic HSCT. The striking feature in all of our patients was the coexistence of eczematous histopathologic features with changes of GVHD. All of the patients had risk factors for the development of chronic cutaneous GVHD: 8 had received a transplant from an unrelated donor, 7 had evidence of extracutaneous GVHD, and at least 5 had a history of acute cutaneous GVHD. We believe there is compelling evidence to suggest that the eczematous dermatosis observed in our patients represents a novel form of chronic cutaneous GVHD that we have named eczematoid GVHD.

The differential diagnosis of a dermatitic eruption occurring after allogeneic HSCT should include the following: an eczematous drug reaction, the precipitation of preexisting dermatitis, or the acquisition of atopic diathesis from donor stem cells. Each potential cause of eczema was considered in our patients. All of the patients were receiving multiple drugs, but none of these were known to be associated with the induction of an eczematous drug eruption. Three patients had allergic disorders and 1 had mild eczema during childhood;
however, the remaining 7 patients had no history suggestive of an atopic susceptibility. None of the patients were known to have another eczematous dermatosis (eg, seborrheic dermatitis or allergic contact dermatitis) before HSCT. Although it is recognized that atopy can be transmitted to an individual from HSCT, none of the donors in this series gave a history of an atopic disorder. We, therefore, suggest that in these patients, eczema, observed both clinically and histopathologically, was expressed as a manifestation of chronic GVHD. Although the pathophysiology of chronic GVHD remains poorly understood, it is recognized that both alloreactive and autoreactive T cells have a role in mediating tissue damage. Thymic injury from acute GVHD may prevent the deletion of autoreactive clones, which can, therefore, promote a range of inflammatory responses. In murine chronic cutaneous GVHD, uncontrolled collagen synthesis is driven by transforming growth factor-β generated by an inflammatory process with a Th2-predominant cytokine profile. In many eczematous diseases, a Th2 response is also typical. A model to explain the development of an eczematous GVH response in our patients will, therefore, need to incorporate the complex interaction between antigen-presenting cells (including epidermal dendritic cells of donor origin) and autoreactive and allogenic T cells stimulated in the presence of Th2 cytokines. External stimuli, most notably, bacterial antigens, will influence the severity of eczematoid GVHD, as with other forms of eczema. Alemtuzumab, a monoclonal antibody that targets CD52 on mature T lymphocytes, was administered to all patients as a part of the conditioning regimen before HSCT. Alemtuzumab-induced T-cell depletion may be central to the development of eczematoid GVHD; however, larger studies are needed to explore the relation between conditioning regimens and GVH reactions.

The development of GVHD after allogeneic HSCT has potential clinical benefits because concomitant graft-vs-leukemia effects can control residual malignancy. In our series, only 1 patient had a relapse of the original hematologic malignancy. Nevertheless, the severity of this form of GVH reaction resulted in substantial morbidity and mortality. All of the patients with eczematoid GVHD developed erythroderma, which was poorly tolerated. The severity of the skin involvement necessitated, in most cases, admission to the hospital for intensive topical therapy and treatment with systemic immunosuppressant agents. Six patients died; in 3, the cause of death was considered to be an infective complication. Three patients had systemic fungal infections, and 1 died of overwhelming bacterial sepsis. In one of these patients, septicemia was probably a complication of intractable skin infection. The need to control the GVHD with systemic immunosuppression therapy may have had a permissive effect in the progression to fatal sepsis. Problems encountered with systemic immunosuppression therapy prompted the use of more effective skin-directed treatment. Six patients were treated with PUVA, and 4 of these responded well, achieving complete cutaneous clearance. Psoralen–UV-A is, therefore, recommended as a useful adjunctive and immunosuppression-sparing treatment in this form of GVHD.

Eczematoid GVHD is a severe, often erythrodermic eruption associated with considerable morbidity and mortality. While this dermatosis represents a complex management problem for dermatologists treating patients with hematologic malignancies, the eczematous phenotype points to immunopathologic pathways previously unexplored in the GVH reaction.

Accepted for Publication: May 3, 2007.

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Author Contributions: Dr Creamer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Creamer, Salisbury, Mufti, and du Vivier.

Acquisition of data: Creamer, Martyn-Simmons, Osborne, Kenyon, Salisbury, Devereux, Pagliuca, Ho, Mufti, and du Vivier.

Statistical analysis: Creamer, Martyn-Simmons, Osborne, Kenyon, Salisbury, Devereux, Pagliuca, Ho, Mufti, and du Vivier.

Obtained funding: Creamer, Martyn-Simmons, Osborne, Kenyon, Salisbury, Devereux, Pagliuca, Ho, Mufti, and du Vivier.

Preparation of manuscript: Creamer, Martyn-Simmons, Osborne, Kenyon, Salisbury, Devereux, Pagliuca, Ho, Mufti, and du Vivier.

Critical revision of the manuscript for important intellectual content: Creamer, Martyn-Simmons, Osborne, Kenyon, Salisbury, Devereux, Pagliuca, Ho, Mufti, and du Vivier.

Table. Treatment and Follow-up of Patients With Chronic Eczematoid GVHD

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Treatment</th>
<th>Response</th>
<th>Duration of Disease, mo</th>
<th>Duration of Follow-up, mo</th>
<th>Outcome; Extracutaneous GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PUVA, prednisolone, tacrolimus</td>
<td>Good</td>
<td>20</td>
<td>24</td>
<td>Remission (skin and blood); no extracutaneous GVHD</td>
</tr>
<tr>
<td>2</td>
<td>PUVA, prednisolone, tacrolimus</td>
<td>Good</td>
<td>17</td>
<td>20</td>
<td>Died (relapse of AML); hepatic GVHD</td>
</tr>
<tr>
<td>3</td>
<td>Prednisolone, cyclosporine</td>
<td>Good</td>
<td>4</td>
<td>4</td>
<td>Died (cryptococcosis); hepatic GVHD</td>
</tr>
<tr>
<td>4</td>
<td>PUVA, methylprednisolone, cyclosporine</td>
<td>Poor</td>
<td>12</td>
<td>12</td>
<td>Died (bacterial sepsis); hepatic and GI tract GVHD</td>
</tr>
<tr>
<td>5</td>
<td>PUVA, prednisolone, cyclosporine</td>
<td>Good</td>
<td>8</td>
<td>12</td>
<td>Remission (skin and blood); no extracutaneous GVHD</td>
</tr>
<tr>
<td>6</td>
<td>PUVA, prednisolone, cyclosporine</td>
<td>Good</td>
<td>6</td>
<td>7</td>
<td>Died (aspergillosis); hepatic GVHD</td>
</tr>
<tr>
<td>7</td>
<td>PUVA, prednisolone, cyclosporine</td>
<td>Poor</td>
<td>9</td>
<td>9</td>
<td>Died (aspergillosis); hepatic GVHD</td>
</tr>
<tr>
<td>8</td>
<td>Prednisolone, MMF</td>
<td>Good</td>
<td>6</td>
<td>42</td>
<td>Remission (skin and blood); bronchiolitis obliterans</td>
</tr>
<tr>
<td>9</td>
<td>Prednisolone</td>
<td>Good</td>
<td>4</td>
<td>4</td>
<td>Died (bacterial sepsis); GI tract GVHD</td>
</tr>
<tr>
<td>10</td>
<td>Prednisolone, tacrolimus, MMF</td>
<td>Good</td>
<td>6</td>
<td>20</td>
<td>Remission (skin and blood); bronchiolitis obliterans</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; GI, gastrointestinal; GVHD, graft-vs-host disease; MMF, mycophenolate mofetil; PUVA, psoralen–UV-A.
istical analysis: Mufti. Administrative, technical, or material support: Creamer, Martyn-Simmons, Osborne, Salisbury, Devereux, and Mufti. Study supervision: Creamer, Salisbury, Ho, Mufti, and du Vivier.

Financial Disclosure: None reported.

Additional Information: The eTable is available at http://www.archdermatol.com.

REFERENCES


Announcement

Manuscript Submission

- Before preparing a manuscript authors should review the Instructions for Authors available at http://www.archdermatol.com.
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- Authors may check the status of their manuscript as it proceeds through the review and decision process by logging into http://manuscripts.archdermatol.com.
- It is important for authors to update their contact information, especially their e-mail addresses, by logging into http://manuscripts.archdermatol.com. Publication of accepted manuscripts may be delayed by our inability to locate authors, who need to approve copy-edited manuscript proofs.
### eTable. Chronic Eczematoid GVHD: Patient and Donor Characteristics

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Diagnosis</th>
<th>Donor Type</th>
<th>CMV Status R/D</th>
<th>Acute GVHD</th>
<th>DLI</th>
<th>Onset of Eczematoid GVHD After Transplantion, mo</th>
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</thead>
<tbody>
<tr>
<td>1/M/54</td>
<td>MDS/RAEB</td>
<td>Unrelated</td>
<td>−/−</td>
<td>Yes</td>
<td>No</td>
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</tr>
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<td>3/M/46</td>
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<td>Sibling</td>
<td>+/−</td>
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<td>Unrelated</td>
<td>−/+</td>
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<tr>
<td>6/F/64</td>
<td>MDS</td>
<td>Unrelated</td>
<td>−/−</td>
<td>No</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>7/M/18</td>
<td>ALL</td>
<td>Unrelated</td>
<td>+/−</td>
<td>No</td>
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<tr>
<td>8/M/54</td>
<td>CMML</td>
<td>Unrelated</td>
<td>+/+</td>
<td>Yes</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>9/M/63</td>
<td>CML/AML</td>
<td>Unrelated</td>
<td>−/−</td>
<td>No</td>
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<tr>
<td>10/M/62</td>
<td>CMML</td>
<td>Sibling</td>
<td>−/−</td>
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</tr>
</tbody>
</table>

**Abbreviations:** ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CMV, cytomegalovirus; DLI, donor lymphocyte infusion; GVHD, graft-vs-host disease; MDS, myelodysplastic syndrome; RAEB, refractory anemia with excess blasts; R/D, recipient/donor; −, negative; +, positive.

*a All patients underwent a conditioning regimen with alemtuzumab (Campath; Genzyme Corp, Cambridge, Massachusetts) and received GVHD prophylaxis.