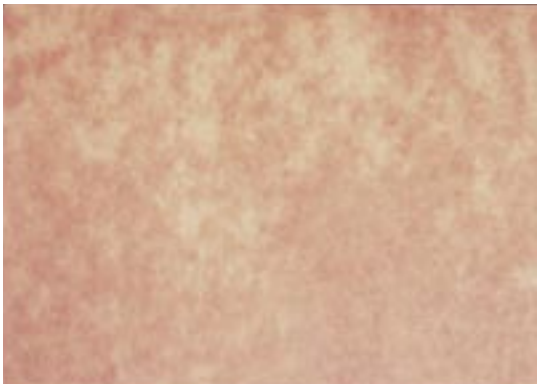
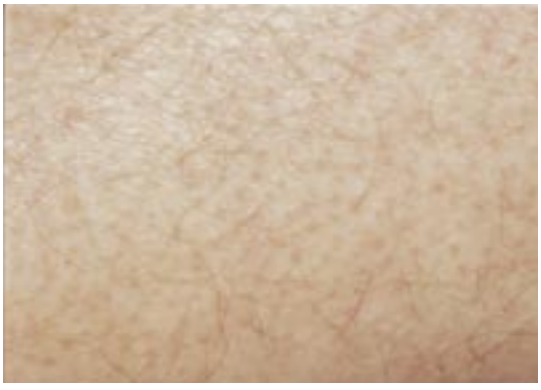
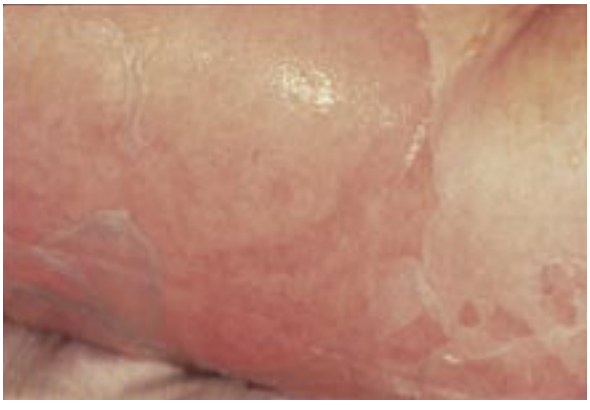
What Is Your Diagnosis?







A patient undergoing a bone marrow transplant developed a new rash. Liver function tests and stool volumes were normal.

PLEASE TURN TO PAGE 236 FOR DISCUSSION

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The author reports no conflict of interest.
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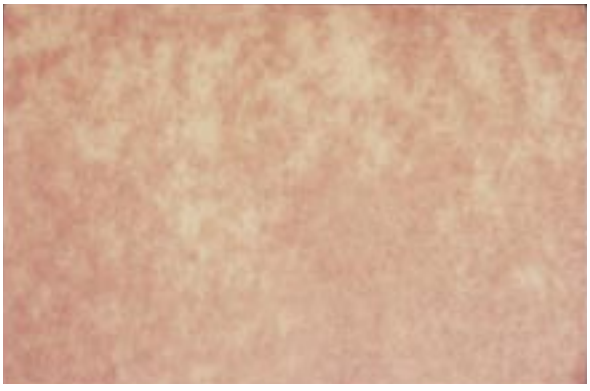
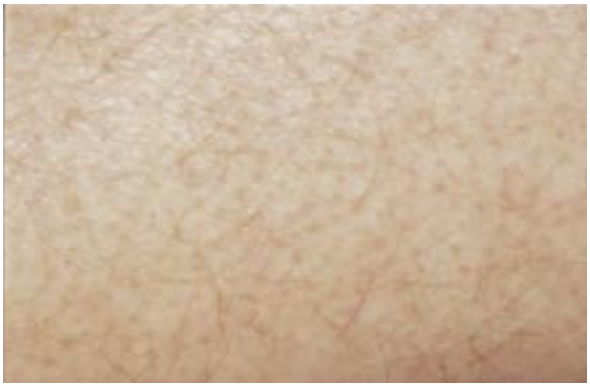
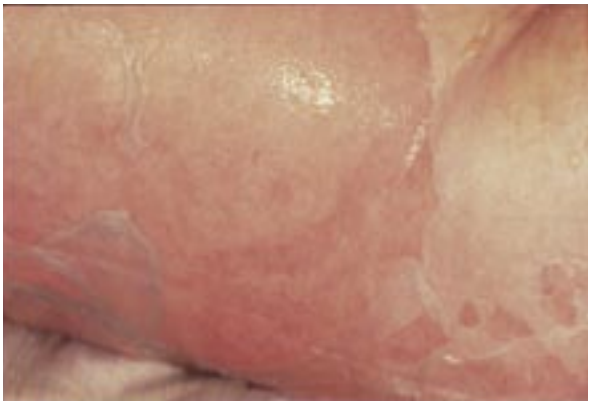
The Diagnosis: Graft-Versus-Host Disease







Skin changes of graft-versus-host disease (GVHD) often precede significant gut, liver, and lung findings. Frequently, the diagnosis of GVHD initially is based on skin findings. Early skin findings generally are confined to the follicular infundibulum and distal portions of the eccrine duct. This focal involvement results in the fine periadnexal papular appearance found in my patient. As the disease progresses, a more diffuse morbilliform rash develops. Periadnexal involvement often is still identifiable as pinpoint foci of deeper erythema. Severe GVHD may progress to grade 4 disease, with a full-thickness loss of skin; this pattern can resemble toxic epidermal necrolysis. Because histologic changes of early GVHD often are focal, it is advisable to examine deeper tissue levels from the paraffin block if adnexal structures are not well represented in the initial sections.

Occasionally, GVHD may present with an eczematous appearance. The eczematous areas can be widespread or can involve the ears, web spaces, and periumbilical skin. The appearance can mimic that of scabies. Biopsy generally will establish the correct diagnosis. Acral keratotic lesions of chronic lichenoid GVHD can mimic palmoplantar warts.[1]

Early diagnosis of GVHD results in prompt institution of appropriate therapy. Intravenous corticosteroids, cyclosporine, and tacrolimus are useful for treating acute GVHD. Dermatologists can play a valuable role in caring for patients who received bone marrow transplants by providing early recognition of suspicious skin lesions and confirming the diagnosis with a skin biopsy. This becomes important in patients with skin lesions preceding liver and gut findings.

It has been reported that tumor necrosis factor α (TNF-α) plays a critical role in the evolution of tissue damage caused by GVHD.[2] The Fas-Fas ligand system appears to be important in the expression of GVHD. It has been reported

that Fas-deficient mice develop more severe cutaneous, intestinal, and thymic disease but less severe hepatic disease than control mice.[3] Also, anti-Fas ligand immunotherapy reduced mortality in a murine model of GVHD.[4] TNF-α, not the Fas-Fas ligand system, appears to be primarily responsible for intestinal cell apoptosis in GVHD. In an animal model, pentoxifylline, an inhibitor of TNF-α, decreased the rate of intestinal crypt cell apoptosis.[5] Measurement of interleukin-10 levels during the aplastic and recovery phases may be useful for predicting the severity of acute GVHD.[6] Expression of CD134, an activation-associated antigen, may be a marker for therapy-resistant GVHD.[7]

A graft-versus-tumor effect is well established for various hematologic malignancies and may be beneficial in patients with breast cancer and other malignancies.[8,9] Evidence suggests that the graft-versus-tumor reaction may be beneficial in some types of lymphoma.[10,11] Customizing prophylaxis against GVHD in patients with early leukemia based on their risk category can maximize the graft-versus-leukemia reaction and improve the 5-year relapse-free survival rate.[12]

The Chinese herbal extract *Tripterygium wilfordii* Hook F has been used successfully to prevent GVHD in a mouse model. The graft-versus-leukemia effect was retained partially despite the absence of GVHD.[13] Interleukin-11 appears capable of separating graft-versus-leukemia reactions from GVHD.[14] Induction of immune tolerance with UVB irradiation of leukocytes can prevent GVHD in a mouse model.[15] Infusion of host hematopoietic cells may be useful in preventing or controlling GVHD.[16] Although it seems attractive to prevent GVHD, the extent of loss of antitumor effect and overall effect on survival require further study.

Although the dermatologist's role in acute GVHD relates mainly to establishment of a diagnosis, in the setting of chronic GVHD, dermatologists often play a central role in therapy. Phototherapy with UVA1 may be effective in some patients with chronic sclerodermatous GVHD.[17] Broadband UVB therapy has been reported to be helpful in the setting of eczematous GVHD.[18] Extracorporeal photophoresis has been shown to induce apoptosis of lymphocytes in patients with GVHD and can be helpful in controlling the disease.[19-21] Phototherapy may prove to be valuable in combination with other agents. Thalidomide has been used for years in chronic lichenoid GVHD. In 1999, sulfasalazine was reported to be effective in the treatment of chronic GVHD.[22] Topical halofuginone, an inhibitor of type I collagen synthesis, may be helpful in chronic sclerodermatous GVHD.[23]

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