EDITORIAL

The "Drug vs Graft-vs-Host Disease" Conundrum Gets Tougher, but There Is an Answer

The Challenge to Dermatologists

ANY DERMATOLOGIST who has been consulted to see a patient who has had a bone marrow transplant (BMT) and then developed a new rash recognizes the difficulty in distinguishing a drug eruption from graft-vs host-disease (GVHD). Over the coming years this is going to be a more, not less, frequent source of frustration for several reasons. Bone marrow transplantation has grown by over 10-fold between 1985 and 1995, and it continues to grow by 10% to 20% annually to more than 15 000 procedures per year worldwide.[1] This is not surprising because BMT is the only hope for survival for many patients with hematologic malignant neoplasms, and improving technology and survival rates have extended the clinical indications considerably. A distinct trend though is that owing to new technologies for suppressing acute GVHD and a lack of perfectly matched donors, more BMT recipients are receiving less closely matched transplants. In combination, these factors mean continued rapid growth in the number of potentially lifesaving transplantations but also ever-higher numbers of patients who will develop acute GVHD or chronic GVHD, with the most commonly affected site being skin.[2]

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Graft-vs-host disease is the major cause of posttransplantation morbidity and mortality, affecting 40% to 60% of allogeneic (nonidentical) transplant recipients.[2] Death rates among those who develop some degree of chronic GVHD vary from 20% for those whose GVHD responds to immunosuppression to 80% for those whose GVHD is refractory to therapy.[3] Because skin is typically the first site of presentation of GVHD, dermatologists are frequently called on to assist in the assessment and management of new rashes in BMT recipients.

Graft-vs-host disease is traditionally divided into acute and chronic forms separated somewhat arbitrarily by whether they occur before or after 100 days after bone marrow infusion. In most cases this criterion is a useful delineation. Acute GVHD has a peak incidence around 30 days after BMT and is composed of a nonspecific erythematous and sometimes pruritic or painful eruption that often first involves a sun distribution prominent on the ears and face or it may present on the palms and soles. If untreated, acute GVHD quickly spreads to confluent erythema of the ears, cheeks, neck, and trunk and can progress to bullous disease and skin sloughing. With prednisone and cyclosporine therapy, acute GVHD usually resolves although it may progress directly to chronic manifestations. Chronic GVHD most often arises around 4 months after BMT and is characterized initially by lichen planus–like papules and Wickham striae that progress to poikilodermatous and often sclerodermatous changes.[2]

CLINICAL DIAGNOSIS IS TRICKY

In the ideal situation, acute GVHD is trivial to diagnose clinically. It would come in the pattern described above roughly 2 or more weeks after allogeneic bone marrow infusion in a patient who has not needed antibiotic agents or other drug therapy that frequently cause rash. (In this case no dermatologist is consulted!) However, because of their similar appearance, acute GVHD is often more tricky to distinguish from drug hypersensitivity. Chronic GVHD is typically less challenging to diagnose as it mimics less common disorders than a drug eruption, such as lichen planus and morphea.

In this issue of the ARCHIVES, Valks et al[4] report unusual presentations of chronic GVHD that might easily be mistaken for drug eruptions. They describe 3 patients who developed nonspecific erythematous eruptions suggestive of a drug rash in the chronic phase of GVHD (>100 days after transplantation). Using the only standard criterion available for GVHD diagnosis, careful clinical follow-up, they show that these rashes were not due to drug or virus and, indeed, were flares of acute GVHD in the chronic phase between 153 and 192 days after transplantation. In all cases, immunosuppression with cyclosporine or corticosteroid therapy had been rapidly tapered prior to the rash's onset, which further supports the diagnosis of GVHD. This article emphasizes that there are no absolute clinical characteristics for declaring a rash to be due to a drug or GVHD.

HISTOPATHOLOGIC DIAGNOSIS IS IMPOSSIBLE

Recently there have been several publications that conclude that histopathology is simply incapable of differentiating a hypersensitivity eruption caused by a drug or virus from the rash of GVHD. Kohler et al[5] retrospectively reviewed 179 skin biopsy specimens from patients who had undergone BMT. They read the slides blinded as to whether these eruptions subsequently developed into GVHD and graded the classic findings of dyskeratotic keratinocytes, basal vacuolization, satellitosis, and necrotic cells in appendages.[5] They found that no single or combined set of these characteristics was able to predict whether the eruption was GVHD. Two other studies evaluated the role of biopsy in affecting clinical

decision making and each concluded that pathologic findings were not helpful in the management of a potential GVHD rash.[6,7] A likely explanation for why there are no reliable distinguishing histological features between drug hypersensitivity and GVHD is that their pathophysiology is mediated by the same cell (T lymphocytes) and they share entirely overlapping phenotypes.

DO EOSINOPHILS MEAN DRUG OVER GVHD? (NO!)

Eosinophils are classically associated with hypersensitivity eruptions and are thought to be suggestive of drug eruptions. One might rely on this finding to help differentiate drug from acute and chronic GVHD, but a closer appraisal suggests this is not wise. In 2 of the 3 cases of GVHD reported by Valks et al,[4] eosinophils were present in the biopsy specimens, which would have wrongly implicated drug as the cause. In addition, in 2 of our own cases of acute-appearing chronic GVHD, abundant eosinophils caused pathologists to favor a drug eruption over GVHD. In both cases the presumption of drug as the cause delayed the initiation of critical immunosuppressive therapy (P.N. and Diego Marra, BA, unpublished data, August 2000). In an analysis of 78 skin biopsy specimens, Massi et al[8] found that eosinophils were present in 3% of the biopsy specimens from patients with acute GVHD and in 5% of the patients who did not have GVHD, suggesting no difference in the prevalence of eosinophils in biopsy specimens from GVHD and from biopsy specimens of rashes from other causes in BMT recipients. These cases suggest strongly that eosinophils are not helpful in distinguishing GVHD from drug eruptions.

IS THERE ANY ROLE FOR BIOPSY FOR A POSSIBLE GVHD RASH?

One rare setting in which biopsy can be highly useful is in a blistering or purpuric eruption to rule out an atypical presentation of infection. Although blistering from drug hypersensitivity may not be easily distinguished clinically from GVHD, herpetic involvement can present atypically in patients with disturbed immune function and is readily diagnosed by pathology. Systemic candidal infection can present as purpuric lesions, but these isolated sites would not likely be confused with a GVHD flare. Skin biopsy may also be useful to document the severity of the eruption over time or for study purposes.

If A DEFINITIVE DIAGNOSIS IS IMPOSSIBLE, WHAT DOES ONE DO?

What does one do with an acute rash after BMT since pathologic findings are unhelpful and the clinical setting can be misleading as described above? Interestingly, one is actually aided in making a recommendation by the consequences of misdiagnosing GVHD. Delaying appropriate therapy for GVHD can be a fatal error. Graft-vs-host disease, especially in the acute form, can progress rapidly over the course of days to severe and deeply entrenched inflammatory damage of the skin, liver, and gut which is irreversible and fatal. Since GVHD can almost never be safely ruled out, one must essentially always presume GVHD and increase immunosuppression, with prednisone therapy usually being more effective than cyclosporine in controlling the acute flare. If the drug history is suggestive of GVHD, it is reasonable to discontinue medications as well, but in the 2 weeks it would take to establish whether drug withdrawal alone is adequate, GVHD can progress substantially. If immunosuppression has been instituted and the rash has responded promptly, a rapid tapering of the drug can be initiated. In cases in which a tapering causes a flare, less toxic therapy than corticosteroids can be substituted such as psoralens plus UV-A or extracorporeal photopheresis. Encouragingly, extracorporeal photopheresis has recently been shown to be effective in controlling GVHD with an excellent safety profile.[9]

A DIFFERENT MINDSET FOR THE DERMATOLOGIST

Dermatologists are accustomed to being able to make a diagnosis, often within seconds of viewing the affected skin. Acute rashes in patients after BMT are thus uncomfortably humbling, and we, as well as our pathology colleagues, are thus tempted to try to make a diagnosis. The reality is, however, although establishing a diagnosis is often possible in retrospect, it cannot be made immediately in many cases. As the cost of being wrong is too great, it is in the interest of our patients that we respond rapidly by presuming GVHD and following up the patient closely as time gives us the answer.

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