
Tissue eosinophils and the perils of using skin biopsy specimens to distinguish between drug hypersensitivity and cutaneous graft-versus-host disease

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Graft-versus-host disease (GvHD) is a frequent and serious complication of bone-marrow transplantation (BMT), and carries a high morbidity and mortality if not promptly recognized and treated. The rash of acute GvHD is often difficult to distinguish clinically from a drug eruption, and skin biopsies are often performed in an attempt to render a diagnosis. Histologically, eosinophils are classically associated with hypersensitivity reactions, and their presence in inflamed tissue is considered suggestive of a drug-induced dermatitis. We present 3 cases of acute exanthema in BMT recipients in whom the presence of eosinophils on skin biopsy specimen led to an initial diagnosis of drug eruption over GvHD. As a result, these patients experienced delays in the institution of definitive immunosuppressive therapy for GvHD. We review the growing literature suggesting that no single or combined histologic feature, including tissue eosinophils, is useful in differentiating GvHD from drug eruptions in BMT recipients. Indeed, in most cases, the cause of a new-onset blanchable erythematous rash in a BMT recipient is most accurately determined by close examination and follow-up of the clinical features without a skin biopsy. (*J Am Acad Dermatol* 2004;51: 543-6.)

The evaluation of acute eruptions in bone-marrow transplant (BMT) recipients poses unique challenges to the dermatology consultant. Patients with severe immunosuppression commonly require multiple medications, many of which are well known to induce cutaneous hypersensitivity. In addition, graft-versus-host disease (GvHD) is a frequent and potentially serious complication after BMT, occurring in up to 50% of patients receiving nonidentical grafts,¹ and carrying mortality as high as 80% if inadequately treated.² Distinguishing between drug eruptions and acute GvHD has far-reaching clinical implications, as the former requires only discontinuation of the offending agent, whereas the latter requires high-dose immunosuppression to avert progression.³

Skin biopsies continue to be used routinely in an attempt to distinguish between these two entities, notwithstanding recent data showing they may be of little clinical use.⁴ We present three BMT recipients in whom overreliance on the presence of eosinophils on skin biopsy specimen resulted in an initial diagnosis of cutaneous drug eruption, delaying initiation of treatment for acute flares of GvHD.

CASE REPORTS

Case 1

A 44-year-old woman with chronic lymphocytic leukemia underwent allogeneic-matched unrelated-donor peripheral blood stem cell transplant after conditioning with fludarabine and busulfan. She received GvHD prophylaxis with cyclosporine, prednisone, and mycophenolate mofetil. On post-BMT day 54 the patient developed fever of unclear origin, for which she received treatment with multiple antibiotics during the following weeks. Shortly after development of symptoms, prednisone and mycophenolate mofetil were tapered and subsequently discontinued.

On post-BMT day 78 the patient developed a generalized pruritic eruption consisting of erythematous macules and papules coalescing into large plaques predominantly affecting her trunk and sparing

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Fig 1. Acute morbilliform eruption that developed on day 209 after bone-marrow transplant involving chest, back, abdomen, arms, and shoulders of 40-year-old woman.

palmoplantar surfaces. At the time, her immunosuppressive regimen consisted solely of cyclosporine (75 mg twice daily, tapered from 300 mg twice daily on admission). A skin biopsy specimen revealed a vacuolar interface dermatitis with scattered eosinophils. These findings were interpreted as favoring a drug eruption, and possible culprit medications were discontinued with no change in her immunosuppressive regimen.

On post-BMT day 83 the rash continued to progress, and focal tense bullae were noted on the anterior aspect of her chest. Mucous membranes and palmoplantar surfaces remained uninvolved, and direct fluorescent antibody testing and cultures for herpes and varicella zoster virus were negative. A tripling of the alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels were noted since onset of the rash. On post-BMT day 86, cyclosporine doses were increased to preadmission levels, and daclizumab, solumedrol, and miconophenolate mofetil subsequently added. The patient's clinical and laboratory status continued to deteriorate, and an endoscopic rectal biopsy specimen on post-BMT day 90 revealed grade IV gastrointestinal GvHD. Despite aggressive immunosuppression, the patient died of associated complications on post-BMT day 118.

Case 2

A 40-year-old woman with chronic myelogenous leukemia underwent an HLA-identical allogeneic BMT from her sister after preparation with total body irradiation. She received GvHD prophylaxis with cyclosporine, at an initial dose of 450 mg twice daily. On post-BMT day 47, prophylaxis against *Pneumocystis carinii* was begun with trimethoprim-sulfamethoxazole, which was given 3 times weekly without interruption and with no reported adverse reactions. She remained at 100% perfor-

mance status, with no evidence of acute or chronic GvHD, and the cyclosporine was progressively tapered to 25 mg once daily on post-BMT day 195, with discontinuation on day 202.

On post-BMT day 209, 1 week after discontinuation of cyclosporine, the patient developed a pruritic morbilliform rash involving her chest, back, abdomen, arms, and shoulders (Fig 1). She had no fever or diarrhea. A skin biopsy specimen showed a lichenoid and interface dermatitis associated with an eosinophil-rich superficial and perivascular inflammatory infiltrate (Fig 2). Based on the presence of eosinophils, the findings were interpreted as consistent with a lichenoid drug reaction, and Dapsone was substituted for trimethoprim-sulfamethoxazole. On post-BMT day 217 the rash was noted to worsen, and the patient was treated with 60 mg of prednisone daily for 3 days and tapered 20 mg every 3 days thereafter. On post-BMT day 230 the patient became ill appearing and jaundiced, with a total bilirubin level of 16 mg/dL, and an alkaline phosphatase level of 248 U/L. The bilirubin and alkaline phosphatase levels had been normal on a visit just before onset of the rash. Despite reinstitution of treatment with prednisone (60 mg/d) and tacrolimus (5 mg twice daily), the patient continued to deteriorate, and died of hepatic complications of GvHD on post-BMT day 258.

Case 3

A 46-year-old woman with non-Hodgkin's lymphoma underwent an HLA-identical allogeneic BMT from her sister after preparation with cyclophosphamide and total body irradiation. She received GvHD prophylaxis with cyclosporine and prednisone beginning on pre-BMT day 1. Skin changes consistent with chronic GvHD were noted beginning on post-BMT day 223, evolving into violaceous papules over the back and buttocks and recurrent oral ulcerations. These findings remained stable and well controlled on prednisone and cyclosporine.

On post-BMT day 600, the patient developed a severe urinary tract infection that resolved after treatment with ciprofloxacin and Pyridium. Subsequently, on post-BMT day 630, the patient developed a distinct new rash consisting of coalescent erythematous papules and plaques involving the legs, thighs, and back aspect of the hands. At the time, her immunosuppressive regimen included cyclosporine (75 mg twice daily) and prednisone (20 mg/d). A skin biopsy specimen revealed marked hydropic degeneration of the basal layer with a bandlike eosinophil-rich lymphohistiocytic infiltrate in the papillary dermis. The findings were

interpreted as consistent with a lichenoid drug reaction.

The eruption initially responded somewhat to emollients and a small increase in prednisone to 30 mg daily; however, by post-BMT day 672 it had evolved to encompass most of her torso and back. The total bilirubin and alkaline phosphatase levels increased from normal at baseline to 2.6 and 157, respectively, and the patient began experiencing significant weight loss despite adequate caloric intake. Administration of prednisone (60 mg/d), FK-506 (5 mg twice daily), and clofazimine beginning on post-BMT day 693 halted progression of the rash and resulted in partial improvement of symptoms.

DISCUSSION

GvHD is a serious and frequent complication after BMT. Clinically relevant acute GvHD occurs in 35% to 50% of patients receiving HLA-identical grafts,¹ and progressive GvHD may carry a mortality as high as 80%.² Acute GvHD frequently begins in the skin, presenting as a morbilliform rash that involves the trunk, neck, cheeks, and ears.⁵ This rash is often difficult to distinguish clinically from drug eruptions or viral exanthems, and skin biopsies are frequently requested in an attempt to narrow the differential diagnosis.

Extracutaneous manifestations of GvHD may involve the liver and gastrointestinal tract,⁵ and are ultimately present in most cases by the late stages of GvHD. Hepatic involvement is manifested by elevated levels of transaminases, alkaline phosphatase, and bilirubin. In particular, total bilirubin more than double the baseline or diarrhea more than 1 L/d are strongly associated with worsening GvHD. When present, evidence of extracutaneous involvement is extremely helpful in pointing toward GvHD when evaluating an acute exanthem in BMT recipients. Unlike in the skin, histopathologic examination of affected liver or intestine can unambiguously confirm the presence of GvHD.

Eosinophils are associated with hypersensitivity reactions, and their presence is consistent with a drug-induced dermatitis.^{6,7} Pathologists and clinicians may, therefore, be influenced by the presence of eosinophils to help distinguish histologically between drug eruptions and GvHD, particularly in the chronic setting (>100 days post-BMT), when an acute eruption is less likely to represent GvHD. Our cases, however, show that eosinophils are not useful in differentiating between drug eruptions and GvHD in BMT recipients.

A number of studies appear to support this conclusion. In an analysis of 78 skin biopsy specimens from patients post-BMT with a new rash,

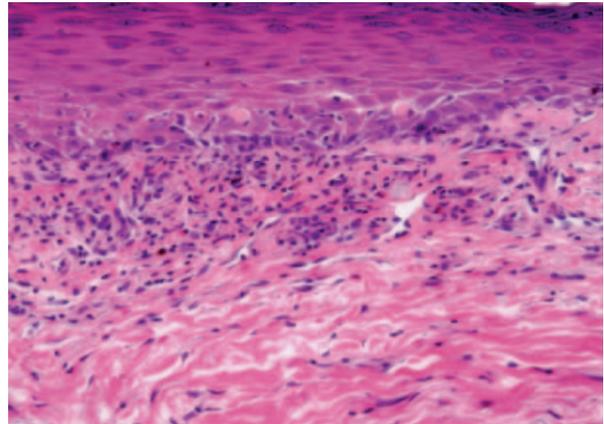


Fig 2. Histopathology of eruption shown in Fig 1, demonstrating lichenoid and interface dermatitis associated with eosinophil-rich superficial and perivascular inflammatory infiltrate.

Massi et al⁸ found that eosinophils were present in 3% of biopsy specimens from BMT recipients with acute GvHD (as defined clinically by the presence of gastrointestinal or hepatic GvHD) and in 5% of biopsy specimens from BMT recipients who did not develop GvHD, suggesting no difference in the prevalence of eosinophils in acute GvHD versus multiple other causes for cutaneous eruptions. Another series of 137 patients postallogeic BMT showed that 4% of patients developing GvHD on clinical grounds had eosinophils present in the infiltrate, whereas none of those without GvHD (48% of sample) showed eosinophils on biopsy specimen.⁹ Eosinophils have also been noted in biopsy specimens from patients with late-appearing GvHD after tapering of immunosuppressive agents.¹⁰ In fact, it has been recently recognized that tissue eosinophilia may be a marker of acute inflammatory flares in GvHD.¹¹⁻¹³ These data strongly suggest that the presence of eosinophils is not a reliable indicator in the histologic differential diagnosis of GvHD.

Recent studies have underscored the limitations of histopathology in this clinical context. In the largest reported series, Kohler et al⁹ retrospectively reviewed 179 skin biopsy specimens from patients post-BMT. Slides were read by two pathologists blinded as to whether these eruptions subsequently developed into GvHD on clinical grounds, and then scored on the basis of 16 histologic parameters, including the presence of dyskeratotic keratinocytes, basal vacuolization, satellitosis, and necrotic cells in the appendages. No single parameter achieved statistical significance on univariate analysis, and a search for histologic characteristics to differentiate GvHD from non-GvHD biopsy specimens using

logistic regression failed to reveal a single best predictor or combination of predictors.

Large doses of cytotoxic drugs and irradiation given in preparation for grafting can also produce histopathologic changes that are indistinguishable from acute GvHD,¹⁴ even in clinically normal skin.¹⁵ In fact, a direct comparison of biopsy specimens from patients with clinical grade I or II GvHD and from healthy and hematologically intact patients with drug-induced dermatitis failed to reveal any morphologic or immunohistochemical differences.¹⁶ A likely explanation for this phenomenon is that the pathophysiology of both processes is mediated by the same effector cell, the T lymphocyte.¹⁷ It is also likely that the skin of patients who are severely immunocompromised has a limited reaction pattern, further contributing to the wide overlap in histologic appearance.

It has been shown that skin biopsies seldom alter the treatment of patients with BMT and a new-onset rash. In one series of 36 biopsies performed to rule out GvHD, 97% were nondiagnostic, and the histologic differential diagnosis (GvHD, drug eruption, and viral exanthem), in fact mirrored the clinical differential diagnosis.¹⁸ Most recently, Zhou et al⁴ have shown that biopsy findings within 30 days of transplantation did not correlate with the clinical severity of cutaneous GvHD, did not impact on the likelihood of patients' receiving anti-GvHD therapy, and had no effect on overall survival at 3 years posttransplant.

Based on these data, it has been suggested that the practice of routinely subjecting post-BMT patients to skin biopsies outside of a research setting may be safely abandoned without compromising care.^{4,19} Our cases further demonstrate that, in BMT recipients with a new rash, eosinophils do not help differentiate between drug eruptions and GvHD in the acute or chronic setting, and suggest that reliance on this histologic finding may confound clinical decision making, resulting in potentially life-threatening delays in the institution of immunosuppressive therapy.

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