Toxic Epidermal Necrolysis in Recessive Dystrophic Epidermolysis Bullosa following Bone Marrow Transplantation

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A 3-year-old child with recessive dystrophic epidermolysis bullosa treated with bone marrow transplantation subsequently developed body-wide epidermal detachment distinct from his epidermolysis bullosa. Toxic epidermal necrolysis was diagnosed by examination and skin biopsy. Although graft-vs-host disease was considered, he had no features of this diagnosis by laboratory studies or skin biopsy, and he improved without addition of further immune suppressants. Throughout the episode, the patient was maintained on cyclosporine A, a component of his transplant regimen, and also a reported therapy for toxic epidermal necrolysis. He had full recovery. Re-epithelialization occurred in a unique folliculocentric pattern, which we postulate was related to the patient’s mesenchymal stem cell infusion, received as an adjunct to his marrow transplantation. (J Pediatr 2016;173:242-4).

Pediatric toxic epidermal necrolysis (TEN) is rare, with the few cases described usually being associated with anti-epileptic medications and antibiotics.1,2 Although hematopoietic stem cell transplant (HSCT) has many well documented risks, TEN within the context of HSCT has only been described a handful of times, with roughly one-half of these cases later reclassified as TEN-like graft-vs-host disease (Stage IV).3,4

Case

A 3-year-old male with recessive dystrophic epidermolysis bullosa status-post myeloablative allogeneic unrelated-donor 8/8 HLA-matched bone marrow transplant and concurrent allogeneic marrow-derived mesenchymal stem cell (MSC) infusion developed a vesiculobullous eruption and epidermal sloughing. His conditioning regimen prior to transplant consisted of infusions of cyclophosphamide, fludarabine, anti-thymocyte globulin, and total body irradiation.

The patient’s course began when he was hospitalized 16 days post-transplant because of fever in the setting of immunosuppression with cyclosporine and mycophenolate mofetil used as standard prophylaxis against graft-vs-host disease. Vancomycin and ceftazidime were initiated empirically, with transition to cefepime after 24 hours. The patient had known previous exposures to all current medications. Blood and urine cultures and a chest radiograph failed to reveal an infectious source for fever.

On hospital day 3, he developed a pink papular rash that rapidly became vesiculobullous with progressive skin sloughing distinct from his epidermolysis bullosa lesions. Additional testing for infection was negative and included cytomegalovirus, human herpes virus 6, Epstein-Barr virus, and adenovirus polymerase chain reaction, Mycoplasma pneumoniae titers, and wound cultures for virus and bacterial. White blood cell count was 1.8 × 10^9/L with an absolute neutrophil count of 1.4 × 10^9/L. Hepatic enzymes were normal. On hospital day 11, a dermatologist noted erythema covering 98% of his body surface area with denuded skin over 90% (Figure 1). No milia or bullae were present and Nikolsky sign was negative. Photophobia, hemorrhagic sloughing of the oral mucosa, and urethral erosions were noted. TEN was confirmed by a biopsy showing full thickness epidermal necrosis with sparse inflammation. The patient had no other extracutaneous findings suggestive of graft-vs-host disease. Engraftment studies of blood reflected partial engraftment with 40% donor derived CD15+ cells and 85% donor derived CD3+ T lymphocytes.

The patient’s medication list was reviewed in an attempt to determine an inciting agent. In the month prior to admission he had been exposed to multiple antibiotics, including levofloxacin, cefazolin, ceftazidime, cefepime, vancomycin, and prophylactic trimethoprim-sulfamethoxazole. He had been previously treated with all agents without incident. Although antibiotic-associated TEN was suspected, a specific agent could not be identified with certainty. All of the potential antibiotic triggers were avoided during his subsequent care. At the time of the TEN diagnosis, all antibiotics were discontinued and intravenous immunoglobulin (IVIG) therapy infusions at a dose of 1 mg/kg/d was initiated for a total of 10 doses. Cyclosporine was continued at the same dose, and mycophenolate was discontinued, as the patient had completed his transplant protocol-determined treatment. Wound care

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included daily dressing changes with sterile saline irrigation and application of silver sulfadiazine cream or mupirocin ointment to denuded areas. Wounds were then dressed with nonadherent gauze.

Three days into the course of IVIG, the patient began to develop diffuse firm, skin-colored, folliculocentric papules (Figure 2). Biopsy of a papule was obtained because of concern for an atypical presentation of cutaneous graft-vs-host disease, which revealed epidermal hyperplasia in the background of a sub-basilar cleavage suggestive of exuberant re-epithelialization and underlying features of epidermolysis bullosa. Within 3 weeks the patient’s skin had returned to his baseline, but he remained hospitalized for an additional two months because of pancytopenia and electrolyte disturbance associated with cutaneous fluid loss.

**Discussion**

Children with TEN fare better than their adult counterparts. In a recent case series of 36 children with TEN treated with IVIG, systemic corticosteroids, or a combination of both, all patients survived. Although adults with TEN in the setting of HSCT have risk of mortality approaching 100% in some case series, it is unclear if this also is true in children.

TEN and TEN-like graft-vs-host disease share similar pathogenic mechanisms, and differentiation is not possible by available laboratory tests. Furthermore, several authors have reported that graft-vs-host disease itself can induce the full spectrum of TEN. Clinical observations and the overall course can help differentiate between these entities. Patients with TEN-like graft-vs-host disease usually have systemic manifestations with evidence of hepatocellular dysfunction and gastrointestinal disturbances, most commonly diarrhea. As our patient had no sustained hepatic abnormalities and only minimal diarrhea despite extensive epidermal detachment, we favor a diagnosis of TEN over graft-vs-host disease. His extensive mucous membrane involvement also supports TEN. The strongest argument against graft-vs-host disease in our patient is his rapid re-epithelialization without increased immunosuppression.

We suspect that treatment with cyclosporine and MSC infusion favorably altered our patient’s clinical course. His concurrent immune suppression with cyclosporine, previously described in small case series as a treatment for TEN, may have decreased initial disease severity and explain his protracted course of desquamation. As noted, the patient was still experiencing progressive skin necrosis 11 days into his hospital stay when first seen by a dermatologist. In most cases of Stevens-Johnson syndrome/TEN, necrosis is rapid and complete by day 4. Cyclosporine can mitigate the inflammatory cascade in TEN by inhibiting interleukin-2, activation of macrophages, and activation of the Fas ligand-Fas receptor pathways.

Despite the patient’s underlying dystrophic epidermolysis bullosa in which scarring in wounds is common place, he healed with minimal scarring. We speculate that MSC infusions aided in skin repair. MSCs are multipotent cells that can be isolated from a variety of tissue sources. They have the unique ability to migrate to injured tissue and promote repair via anti-inflammatory, antimicrobial, and pro-angiogenic immune modulating properties. In a mouse model, MSC infusion decreased excessive scar formation. MSCs were reported to produce rapid wound healing in 3 patients with drug-induced TEN refractory to standard treatments. There were no adverse events associated with MSC infusion in the patients with TEN and only mild transfusion reactions reported in other studies utilizing MSCs.
The patient’s recent MSC infusion may also help explain his unique re-epithelialization pattern. The bulge region of the hair follicle is a known keratinocyte stem cell reservoir. In TEN, the follicular unit is relatively spared from necrosis compared with other skin appendageal structures.16-19 Most cases of TEN, however, do not re-epithelialize with the folliculocentric pattern seen in our patient. Perhaps a better explanation would be re-epithelialization arising from the MSC, which are also located in the follicular unit. Specifically, the connective tissue sheath surrounding the follicle is the anatomic niche of MSCs.20-24 Both bone marrow MSCs, as infused into our patient, and hair follicle dermal MSCs express the same surface markers.24 In a mouse study, infused labeled marrow-derived MSCs localized to hair follicles, sebaceous glands, and blood vessels. MSCs that were incorporated into follicles and sebaceous glands were positive for pan-cytokeratin.25 We speculate that in the setting of tissue injury from TEN, the patient’s infused MSCs homed to their natural locations in the appendageal structures to aid in the re-epithelialization process.

References