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Treatment of Severe Drug Reactions by Hemodialysis

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Abstract

Background—Extracorporeal treatments such as hemodialysis and plasma exchange are lifesaving measures in the treatment of drug poisoning. This treatment method generally is not used for severe cutaneous and systemic drug reactions.

Methods—Here, we describe 3 cases wherein hemodialysis therapy was instrumental in reversing the adverse drug reaction.

Results—In the cases of severe cutaneous drug reactions reviewed, patients presented with linear immunoglobulin A bullous dermatosis, acute generalized exanthematous pustulosis, and toxic epidermal necrolysis. Salvage treatment with hemodialysis therapy drastically influenced the course of disease, resulting in remission.

Conclusions—This novel and highly effective treatment option is not considered in current algorithms for adverse drug reactions. Hence, in addition to the rarity of these reactions, the main limitation of the study is the small number of patients. Hemodialysis can substantially alter the prognosis and, in some cases, be a lifesaving treatment for patients with severe adverse cutaneous drug reaction associated with systemic toxicity.

Introduction

The term adverse drug reaction refers to any adverse event that occurs in a patient taking a medication at the correct therapeutic dose and for the correct medical indication. Drug adverse events may affect any organ in the body and are frequently accompanied by skin involvement, generally termed a drug rash^{1,2}. This reaction is an immediate or delayed hypersensitivity reaction to a specific medication. Most medication-related skin rashes are relatively easy to identify. Presentation mainly involves a morbilliform or urticarial rash, and the offending agent is identified by a temporal relationship to intake. The patient's record then is updated to indicate an allergy to the medication.

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A severe cutaneous adverse reaction (SCAR) to drugs³⁻⁸ is rare but may include Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, linear immunoglobulin A bullous dermatosis (LABD), acute generalized exanthematous pustulosis (AGEP), and toxic epidermal necrolysis (TEN). Other reactions are generalized erythroderma and capillary leak syndromes. Systemic manifestations of these severe reactions include kidney and liver injury, which may delay and aggravate clearance of the offending agent. Dermatologists can emergently diagnose the type of rash via clinical and histopathologic evaluations. Standard treatment for these patients relies on identifying and removing the causative agent, administering corticosteroids or immunomodulators, and providing supportive care.

Severe reactions occur mostly in hospitals, where the patient may be on a multidrug regimen. Identification of the causative agent may be more difficult in this setting, particularly when antibiotics are changed swiftly based on microbiologic sensitivities. If the suspected drug or agent is not correct, then the true offending agent continues to circulate. In this cycle of injury, the subsequent organ impairment then diminishes the patient's ability to clear the agent. In this process, multiorgan damage with kidney and liver involvement may increase risk of potentially fatal consequences. Extracorporeal treatment approaches such as hemodialysis or plasma exchange can potentially be lifesaving during acute events, as in the case of drug poisoning⁹⁻¹¹. However, these measures are rarely used for SCAR. Herein, we describe 3 patients with different SCAR presentations associated with systemic manifestation. All responded promptly when dialysis was used to remove the offending agent.

Report of 3 Cases

Case 1

A 71-year-old obese white woman was admitted with necrotizing pancreatitis and severe sepsis. During her 6-week stay in the intensive care unit (ICU) for multiorgan failure, she required vasopressor support, activated protein C, numerous antimicrobial agents, tracheostomy, and renal replacement therapy in the form of continuous venovenous hemofiltration. After 6 weeks in the ICU, she was transitioned to a step-down unit. Two days after her discharge dermatology was consulted for a skin rash. The eruption was initially morbilliform but worsened to erythema, edema, and large bullae involving the back, chest, and lower extremities (Figure 1A). The primary team initiated daily intravenous methylprednisolone (125 mg/day) without improvement. Biopsies showed subepidermal bullae with neutrophilia (Figure 1B), and direct immunofluorescence assays showed linear immunoglobulin A (IgA) deposition at the basement membrane zone. These findings were consistent with a diagnosis of LABD.

A drug timeline showed that she had received vancomycin, meropenem, and furosemide while in the ICU. Of the 3 drugs, vancomycin was the drug most commonly associated with LABD and was presumed to be the primary culprit. Medication review showed daily vancomycin doses for 3 days preceding her discharge from the ICU. Despite treatment with systemic corticosteroids and triamcinolone cream, new bullae continued to form. Circulating vancomycin level, measured 7 days after receiving the last dose, surprisingly yielded a

therapeutic drug level of 14.5 mcg/mL. The persistently high level of the drug was attributed to diminished clearance after relapse of an acute kidney injury (serum creatinine, 2.6 mg/dL).

Because of the refractoriness of her adverse drug reaction, kidney dysfunction, and persistently elevated vancomycin drug levels, a nephrologist was consulted for hemodialysis therapy. Although vancomycin is not generally deemed dialyzable through conventional hemodialysis^{12–14}, intermittent hemodialysis using a high flux dialyzer membrane was initiated. After 3 daily treatments of hemodialysis and/or diafiltration/ultrafiltration for volume removal, vancomycin levels decreased to <5 mcg/mL and the patient's rash markedly improved in a 24- to 48-hour period (Figure 1C). Follow-up 8 years later shows that she is alive and well.

Case 2

A 60-year-old white man was transferred from another hospital with minimal records. The patient had altered mental status, a history of alcoholic liver disease, and was hospitalized for rhabdomyolysis-induced kidney failure (creatinine, 2.1 mg/dL) and anasarca that was not considered severe enough to warrant dialysis. The patient had a progressive rash with leukocytosis, described by as an erythematous eruption in dependent areas. The furosemide and cefepime he was receiving on admission were discontinued.

A dermatologist was consulted when large sheets of the patient's skin began sloughing off and copious serous drainage from his skin was observed in dependent areas. The fluid extravasation was deemed attributable to anasarca, imitating a capillary leak syndrome. Clinically, the patient had generalized erythroderma with edema, a palpable vesiculopustular eruption in the axilla and flexural arm as shown in figure 2A. The dependant areas showed extensive sloughing of the skin with fluid leakage (Fig 2B). Mucosal and genital skin was uninvolved. The differential diagnosis was a drug reaction versus skin sloughing secondary to fluid leakage. A biopsy from the erythematous vesicular and pustular skin showed interface dermatitis with neutrophil involvement in the dermis and epidermis (Figure 2C1) and subcorneal pustules (Figure 2C2). This is consistent with a diagnosis of AGEP with a EuroSCAR score of 9 which is definite for AGEP (typical pustules, erythema, and distribution pattern, presence of PMN>7k/mm², subcorneal and intraepidermal non-spongiform pustules without papillary edema. A 9 score is definite for AGEP). The direct immunofluorescence assay was negative.

In view of the progressive kidney and liver dysfunction, in addition to the refractory rash, a nephrologist was consulted. The patient was treated with intermittent hemodialysis and diafiltration therapy for additional volume removal. After 2 sessions, using a high flux dialyzer membrane, his skin rash resolved (Figure 2D) and he had rapid improvement in liver and kidney function and improved mental status. He was discharged from the hospital after 5 days. Follow-up 1 year later shows that he is alive and well.

Case 3

A 63-year-old white man was admitted to the ICU after appearing ill at his outpatient hemodialysis center. He had a history of congenital spina bifida and end-stage renal disease

on thrice-weekly hemodialysis therapy. At admission, he had acute-on-chronic respiratory failure in the setting of right lower lobe pneumonia, methicillin-resistant *Staphylococcus aureus* bacteremia with subsequent septic shock, and altered mental status. He required mechanical ventilation for respiratory failure. On day 1 of his hospitalization, he was started on a course of linezolid and piperacillin-tazobactam. This regimen was discontinued because of thrombocytopenia on day 5, at which point he was transitioned to ceftriaxone (continued until day 7) and vancomycin (continued until day 10 and then restarted on day 12).

A dermatologist was consulted on hospitalization day 7 for generalized bullae and persistent skin sloughing over several days. Skin examination showed dusky erythema and tense bullae, along with erosions, affecting over 30% of the patient's body surface area (Figure 3A). Hemorrhagic crusting of the mucosa, without ocular involvement, was observed. Biopsies performed on the day of the initial consultation showed (on routine hematoxylin and eosin staining) vacuolar interface changes, with scattered apoptotic keratinocytes, and focal full-thickness epidermal necrosis, consistent with Stevens-Johnson syndrome or TEN (Figure 3B). Direct immunofluorescence was consistent with a lichenoid tissue reaction.

After histopathology results were known, the patient was immediately treated with intravenous immunoglobulin (2 g/kg on days 9–10). The offending medication was not clearly established, but ceftriaxone or piperacillin-tazobactam (or both) was believed to be the most likely precipitants of the patient's TEN. Importantly, hemodialysis was prematurely terminated on the day of admission (hospitalization day 1) because of intradialytic hypotension due to high-grade bacteremia. Hemodialysis using a high flux dialyzer membrane was resumed on days 3 and 4 of hospitalization, when the patient was hemodynamically stable. Hemodialysis was again withheld on days 5 through 7 to allow a catheter-free period (to treat catheter-associated bacteremia) and was not performed again until day 8. Temporal improvement of the skin lesions was noted after each dialysis session.

The patient's skin progression ultimately stabilized, with no new bullae forming on days 10 to 12. From day 13 onward, he had gradual but steady improvement of skin lesions, as shown by re-epithelialization (Figure 3C).

Unfortunately, the patient never recovered and required mechanical ventilation, vasopressor hemodynamic support, and transition to continuous veno-venous hemofiltration. Given the recurrent complications associated with acute-on-chronic, hypoxemic, and hypercarbic respiratory failure and poor prognosis, his family transitioned him to comfort care. He died on hospital day 18.

Discussion

The 3 cases described here show the potential benefit of extracorporeal therapy in the form of hemodialysis in the treatment of patients with refractory SCAR. For all 3 patients, a temporal relationship was observed wherein bullae formation ceased only after the initiation of hemodialysis therapy. Thereafter, remission of both SCAR and multiorgan dysfunction occurred.

Hemodialysis is one of many procedures classified as extracorporeal therapy; others include plasmapheresis, plasma exchange therapy, hemodialysis, peritoneal dialysis, and continuous venovenous hemofiltration. This large field in medicine is under the purview of nephrologists and hematologists, but dermatologists should be aware of the potential benefits implicit in this approach. The procedure used may differ according to the drug in question. In the decision-making process, the underlying characteristics of the offending agent and the extracorporeal therapy should be considered. Each extracorporeal modality has varying capability for drug removal. The rate of drug clearance is affected by the molecular weight, protein-binding ability, water solubility, volume of distribution, and plasma clearance. For example, vancomycin has a varying volume of distribution (increases with kidney dysfunction and obesity) and protein-binding ability (decreases with kidney dysfunction) and is generally not deemed dialyzable by conventional hemodialysis^{12–14}. However, in our experience, closely repeated hemodialysis sessions helped clear vancomycin and were associated with rapid improvement of the skin condition.

It remains unclear whether hemodialysis optimized SCAR treatment primarily through clearance of the offending agent or also through other off-target effects such as removal of uremic toxins contributing to cellular dysfunction or other unidentified offending agents. Extracorporeal therapy is not without risks, including risks associated with placement of a large-bore catheter, catheter-associated infection, or adverse reactions to dialysis or plasma exchange procedures. However, the benefits inherent to such interventions may outweigh these risks because they can alter the trajectory of disease progression.

More information and guidelines are forthcoming. An international group, the Extracorporeal Treatment in Poisoning workgroup, consists of nephrologists, pharmacists, and toxicologists who are in the process of developing evidence-based guidelines on how and when to use extracorporeal techniques in the approach to drug poisoning. Excellent articles about these topics have been published^{9–11}. Although SCAR is an immunologically mediated reaction to drugs given in therapeutic doses, these doses may accumulate in the circulation when renal or liver clearance is impaired. In that respect, SCAR is similar to drug poisoning, in which the adverse reaction is due to an acute drug overdose.

We present these 3 cases to aid in the care of patients with SCAR. In every published case series describing these rashes, systemic involvement was noted and mortality rates were high, specifically in TEN and Stevens-Johnson syndrome^{7,15}. Howard et al¹⁶ reported a similar situation involving a cancer patient receiving high-dose methotrexate that resulted in toxicity; the patient improved after hemodialysis. Generally, morbidity and fatality in cutaneous adverse diseases is not directly caused by the skin disease but to the complications of organ injury and sepsis, wherein skin denudation allowed microbial entry into the circulation.

Patients with SCAR have increased risk of death because they frequently have systemic involvement with multiorgan dysfunction. Notably, these same individuals may have greater susceptibility to adverse drug reactions because of underlying genetic alterations in drug metabolic pathways^{17–19}. Therein, pharmacogenomic testing has a potential role in secondary prevention. For acute management, responses to corticosteroid therapy and to

discontinuing the suspected offending agent alone are often poor. The addition of other treatments such as intravenous immunoglobulin therapy, calcineurin inhibitors (eg, cyclosporine) or tumor necrosis factor- α may not be sufficient^{20–22}. In these refractory cases with evidence of kidney or liver dysfunction, clearance of the offending agent is suboptimal and the cycle of injury continues. Aggressive treatment such as extracorporeal therapy may be indicated to optimize clearance of the offending agent(s), expedite skin and multiorgan healing and recovery, and improve the prognosis associated with SCAR. However, consideration should be given to the potential complications associated with hemodialysis and ultrafiltration/diafiltration therapy.²³ Risks of this treatment and the procedures required to perform it may include: pneumothorax from catheter placement, catheter-associated venous thrombosis, catheter-associated blood stream infection, in addition to the dialysis-treatment associated alterations in hemodynamics, post-dialysis recovery, and heart rhythm disturbances with electrolyte shifts. These and other risks should be carefully considered and subsequently weighed against the potential benefits of extracorporeal treatment.

Our recommendations (level IV evidence) are as follows:

1. SCAR and other severe rashes should be identified quickly through consultation with a dermatologist; skin examinations, biopsies, and immunofluorescent studies should be done emergently to determine the type of skin disease. It can be confusing initially, even to dermatologists, particularly when bullae, blisters, or denudations of the skin are present. This pattern can be seen in all SCAR-related rashes.
2. If the offending agent is identified, it should be omitted from the drug regimen. Standard supportive skin care should be provided, with or without concomitant corticosteroid or immunomodulator therapy.
3. If the offending agent is difficult to identify (as in the above cases) and the patient continues to worsen both systemically and cutaneously, then a nephrologist should be consulted for consideration of extracorporeal therapy such as dialysis, plasmapheresis, or continuous renal replacement therapies, especially for patients with renal and hepatic dysfunction.

Limitations

The limitations of the study include the small number of patients and the rarity of these adverse drug reactions. We hope that these findings will lead to prospective studies to confirm the validity and safety of such procedures, which will require collaboration with nephrologists and hematologists.

Conclusion

Extracorporeal techniques can be used to assist in removal of the toxic agent, similar to lifesaving measures used with drug poisoning. These techniques can help tremendously when a patient has a severe drug rash and systemic toxicity but the offending agent is not

clearly established. We suggest that dialysis should be added as a potential option in the treatment algorithms of SCAR.

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Abbreviations

AGEP	acute generalized exanthematous pustulosis
ICU	intensive care unit
LABD	linear immunoglobulin A bullous dermatosis
IgA	immunoglobulin A
SCAR	severe cutaneous adverse reaction
TEN	toxic epidermal necrolysis

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Figure 1. Linear Immunoglobulin A Bullous Dermatitis

A, Erythema, edema, and blisters are seen on the patient's back. Residual serum vancomycin level, measured 7 days after the last dose, was still within the therapeutic range (14.5 mcg/mL). B, Biopsy from the neck shows subepidermal clefting with papillary neutrophilia (hematoxylin-eosin; original magnification, $\times 40$). C, Total clearing of erythema and healing of bullae at a vancomycin level < 5 mcg/mL.

Figure 2. Acute Generalized Exanthematous Pustulosis

A–B, The patient had erythema and anasarca of the abdomen and sheets of superficial skin denudation on the back in dependent areas. C, Histopathologic evaluation showed intraepidermal and dermal neutrophils in figure C1 (hematoxylin-eosin; original magnification, $\times 10$) and neutrophils in the superficial epidermis with subcorneal pustules in figure C2 (hematoxylin-eosin; original magnification $\times 40$). D, Resolution of erythema, edema and healing of denuded skin after hemodialysis.

Figure 3. Toxic Epidermal Necrolysis

A, Severe crusting caused denudation. B, Subepidermal bulla and interface dermatitis (hematoxylin-eosin; original magnification, $\times 10$). C, Re-epithelialization of skin.