CLINICAL VIGNETTE

Toxic Epidermal Necrolysis

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Case Report

A 79-year-old male with diabetes, hypertension, gout, and chronic kidney disease was brought to the emergency department (ED) with a severe skin rash. Three weeks prior to presentation, the patient noted diffuse pruritus. One week before he was admitted to an outside hospital with worsening renal failure, metabolic acidosis, and hyperkalemia, and started on hemodialysis. At discharge his allopurinol, amlodipine, clotrimazole, hydralazine, and sodium citrate were discontinued. In addition, at hemodialysis the day prior to presentation, his furosemide, metoprolol, and tamsulosin were discontinued. He remained only on ferrous sulfate and acetaminophen. Since his outside hospitalization, the patient developed progressively worsening dry, scaly, flaky skin changes all over his body, with areas of skin sloughing on the day of presentation. The patient's wife reported increasing confusion and agitation during the past week, which she attributed to starting hemodialysis. The patient denied any complaints other than fatigue and malaise.

On arrival to the ED, the patient's vital signs included a temperature of 35.9 degrees Celsius, heart rate of 80, respiratory rate of 20, blood pressure of 103/55, and an O2 sat of 100% on room air. He was cachectic, drowsy but arousable, pupils were equally round and reactive, oral mucous membranes were dry with few mucosal erosions. There were multiple patchy areas of desquamation involving 10-30% of body surface area (BSA) with underlying erythematous and weeping skin. He was oriented only to self and place, answering simple questions with short statements, but otherwise had a nonfocal neurologic exam. There was an intact right internal jugular tunneled hemodialysis catheter and a recently placed left upper extremity arteriovenous fistula, both without discharge, tenderness to palpation, or surrounding erythema. The rest of physical exam was unremarkable.

On laboratory examination, the patient was found to have a sodium of 145 mmol/L, potassium of 4.0 mmol/L, blood urea nitrogen of 55 mg/dL, creatinine of 4.91 mg/dL, calcium of 7.9 mg/dL, white blood cell count of 1.8 k/uL, hemoglobin of 9.0 g/dL, platelet count of 49 k/uL, lactate of 3.6 mmol/L, pH of 7.27 and partial pressure of carbon dioxide of 42 mmHg on venous blood gas analysis. Liver function tests, troponin, coagulation factors, urinalysis, electrocardiogram, and chest xray were unremarkable.

Based on the observed diffuse skin changes, with desquamation and involvement of the mucous membranes, a presumptive differential diagnosis of toxic epidermal necrolysis/Stevens-Johnson syndrome versus toxic shock syndrome was made. The patient was started on broad spectrum antibiotics and aggressive fluid resuscitation. A punch biopsy was compatible with toxic epidermal necrolysis, thought to be secondary to increased allopurinol levels from recent renal failure. The patient's skin desquamation progressed rapidly to affect >75% of BSA. The patient also had decreasing blood pressure and multi-organ failure despite aggressive fluid hydration and vasopressors. Ultimately, the family chose comfort care in the face of a grave prognosis and the patient died shortly thereafter.

Discussion

Toxic epidermal necrolysis (TEN) is a life-threatening skin disorder characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes. There is growing consensus that Stevens-Johnson syndrome (SJS) and TEN are a single disease with common causes and mechanisms. In SJS, there is <10% of BSA involved, with widespread blistering, but limited confluence of individual lesions and epidermal detachment. Overlap SJS/TEN is characterized by 10-29% of BSA involvement, with confluent blisters and full epidermal detachment and erosions. TEN is the most severe form of desquamative skin reaction, defined as epidermal detachment of > 30% of BSA [1]. The incidence of severe exfoliative skin reactions are estimated at 0.4-1.5 cases per million person-years [2]. They can occur at any age, but are seen more frequently in persons over 60 years of age, and more frequently in women than in men. Mortality ranges from 30-50% in TEN [3].

The pathogenesis and etiology of TEN is incompletely understood. The widespread epidermolysis results from keratinocyte apoptosis [4]. Several immunopathologic pathways leading to keratinocyte apoptosis in TEN have been proposed, including Fas ligand activation on keratinocyte membranes to receptor-mediated apoptosis [5], release of destructive perforin and granzyme B from cytotoxic T cells generated from an interaction with major histocompatibility complex class I-expressing cells [6], overproduction of T cell and/or macrophage derived cytokines [7], and drug-induced

secretion of granulysin from cytotoxic T cells and natural killer cells [8]. There are also genetic factors that have been found to influence development of TEN. HLA-B*5801 and HLA-B*1502 seem to increase risk for SJS/TEN in Han Chinese, while HLA-B12 seems associated with improved survival from TEN [9-11]. Finally, HIV-positive individuals seem to have an increased risk for developing TEN [12].

In the majority of adult cases, TEN is triggered by a preceding medication [13,14]. Since the various proposed pathogenic mechanisms are not IgE mediated, a desensitization of the triggering drug is not an option. The most common offending classes of medications include anti-gout agents, antibiotics, antipsychotics and antiepileptics, and analgesics and non-steroidal anti-inflammatory agents (NSAIDs). Roujeau et al. found the risk for developing SJS and TEN was highest with sulfa antibiotics (relative risk (RR) 172), followed by chlormezanone, cephalosporins, quinolones, and aminopenicillins [15]. Amongst medications likely to be prescribed for long term use, the risk was highest in the first two months. Other drugs with high RRs included carbamazepine, oxicam-NSAIDs, corticosteroids, phenytoin, allopurinol, phenobarbital, and valproic acid. Another study showed strong associations for new drugs such as nevirapine, tramadol, pantoprazole, lamotrigine, and sertraline [16]. In this case, the patient's trigger likely was from his allopurinol use, compounded by his recent decline in renal function.

The acute mucocutaneous reaction is characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes resulting in exfoliation and possible sepsis and death. Initial differential diagnosis may include other severe bullous skin diseases such as staphylococcal scalded skin syndrome, toxic shock syndrome, phototoxic skin reactions, drug reaction with eosinophilia, acute generalized exanthematous pustulosis, or paraneoplastic pemphigus. Lesions are flat and tender, resembling target lesions but of larger size, often coalesce, and may exhibit a positive Nikolsky sign (epidermal separation induced by gentle lateral pressure on the skin surface). Oral mucosal lesions are typically present. There may be other organ system involvement, commonly in the ophthalmologic, genito-urinary, and pulmonary systems. Ophthalmologic involvement includes conjunctival lesions, excessive tearing, and hyperemia. Genito-urinary involvement includes urethritis, which may result in urinary retention. Pulmonary complications may include bronchial hypersecretion, pulmonary edema, and bronchiolitis.

Recognition of potential cases of TEN is critical. Immediate discontinuation of the triggering medication improves mortality [17]. The management of TEN consists primarily of supportive care. This supportive care is similar to the treatment of extensive burns, and includes wound care, fluid and electrolyte management, nutrition, ocular care, temperature and pain control, and monitoring for superinfections. Early transfer to a burn unit reduces morbidity and mortality [18,19].

Beyond supportive care, there are various adjunctive therapies that are frequently used based on small studies, but not universally accepted due to a lack of controlled trials, including glucocorticoids and intravenous immunoglobulin (IVIG). A large multinational retrospective study of both SJS and TEN patients demonstrated a nonsignificant trend towards diminished mortality with the use of steroids and no significant mortality difference with use of steroids or IVIG or both [20]. Cyclosporine is another immunosuppressant agent sometimes used, which is thought to inhibit downstream cytotoxic epidermal apoptosis through either the Fas ligand or the perforin-granzyme pathway [21]. Case reports support plasmapheresis use, thought to be removing a toxin or cytotoxic mediator leading to TEN [22]. The only randomized, double-blind, placebo-controlled trial concerning treatment of TEN was performed for thalidomide [23]. It showed increased mortality in the thalidomide group versus placebo.

A severity of illness score (SCORTEN) calculated on day 3 of hospitalization estimates the risk of death in toxic epidermal necrolysis has been validated [24]. This score combines seven independent risk factors for mortality (age >40 years, heart rate > 120 beats/min, history of cancer or hematologic malignancy, involved BSA >10%, blood urea nitrogen level > 10 mmol/L, serum bicarbonate level < 20 mmol/L, and blood glucose level > 14 mmol/L). With one point per item, the predicted mortality ranges from 3% for 0-1 points, to 90% for ≥ 5 points.

For those patients who survive TEN, there are potential long-term sequelae, including dermatologic, ocular, and pulmonary complications [25]. Dermatologic sequelae are the most common and include scarring, irregular pigmentation, alopecia, and abnormal regrowth of nails. Ophthalmologic sequelae include dry eye, neovascularization of the cornea, corneal scarring leading to blindness, and scleritis. Long-term pulmonary complications may include bronchiectasis and chronic bronchiolitis [26].

In summary, toxic epidermal necrolysis is a serious acute desquamative mucocutaneous reaction that can involve multiple organ systems with a high mortality rate. Awareness of possible offending drugs is important for early recognition, particularly as discontinuation of the offending agent improves mortality. The mainstay of treatment for TEN is supportive care. Various immunosuppressive adjunctive therapies are commonly utilized, including glucocorticoids, IVIg, cyclosporine, and plasmapheresis. More research is needed on adjunctive therapies, in the form of randomized, controlled trials.

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