CLINICAL VIGNETTE

A Case of Steven's Johnson's Syndrome/Toxic Epidermal Necrolysis after Trimethoprim/Sulfamethoxazole Use

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A 43-year-old woman with no prior medical history presents with rash for the past four days. She awoke with bilateral eye redness four days ago accompanied by mild clear discharge. There were no vision changes, pain, itchiness, or preceding upper respiratory symptoms. She began developing a rash that was mostly erythematous and popular, later progressed to vesicles beginning in her chest, and then spread to her back, face, and limbs. One day ago, she developed oral pain. She had no fever, chills, chest pain, or shortness of breath. She does not feel throat tightness or swelling. She has not traveled recently.

The patient has no prior medical problems and takes no chronic medications. She has no allergies. Two weeks ago, she developed vaginal itching and dysuria after having sex with her boyfriend. She reported a latex allergy and a latex condom was used. Nonetheless, she was diagnosed with a presumptive urinary tract infection in addition to cellulitis from a mosquito bite and started on trimethoprim/sulfamethoxazole DS twice daily and cephalexin 500 milligrams twice daily. She was on day 8 of 10 when her symptoms began.

On exam, she was a petite Hispanic female in no acute distress. Vital signs showed temperature of 37.9C, heart rate 91, respirations 20, blood pressure 100/57, and oxygen saturations 100% on room air. There was an obvious maculopapular rash most notably on her chest and back with some confluent areas. Additionally, there were <1cm vesicles overlying the rash in the chest and face. Nikolsky's sign was positive. Exam demonstrated bilateral conjunctival injection but no chemosis. There was no corneal fluorescein uptake. Eyelids were edematous. Lips and buccal mucosa showed mild ulceration. The rest of her exam was unremarkable.

The patient was given intravenous fluids, solumedrol, morphine, and ondansetron in the Emergency Department prior to being admitted to the intensive care unit. Biopsy of the skin showed apoptotic keratinocytes and clefting along the epidermal/dermal junction, consistent with Steven's Johnson's syndrome. Dermatology consultation recommended initiation of etanercept and continued solumedrol. Otolaryngology was consulted and recommended erythromycin ophthalmic ointment. Gynecology was also consulted for management of vaginal lesions and topical betamethasone was initiated. The patient's skin lesions improved, and she was eventually discharged after 16 days in the hospital. At follow up, the patient had fully recovered with minimal scarring.

Discussion

Steven's Johnson's Syndrome is a rare, life threatening dermatological condition that is characterized by an erythematous rash followed by blister formation and desquamation of the skin. The spectrum of disease includes Steven's Johnson's syndrome (SJS), Toxic Epidermal Necrolysis Syndrome (TENS), and an overlap entity of SJS/TENS. In each of these conditions, there is <10%, >30%, and 10-20% desquamation, respectively. Additionally, more than 90% of cases are associated with mucocutaneous involvement, involving the ocular, oral, or genital areas.[1,2] A prodrome of nonspecific symptoms including fever, odynophagia, and eye pain precedes the rash. The rash tends to be erythematous macules that can rapidly coalesce beginning in the sternal region, face, palms, and soles. Development of symptoms usually occurs between one and four weeks after exposure.[2-4] However, symptoms have occurred as early as 24 hours after exposure of a drug, likely due to re-exposure of drug that was previously taken.[5] Previously, SJS and TENS were thought to be in a spectrum with erythema multiforme major (EMM), but actually, these diseases differ. A large retrospective study by the SCAR group showed that EMM is highly associated with HSV infections, while exposure to drugs was more prominent in SJS and TENS.[6]

SJS and TENS were first described by Alan Lyell in 1956 after recognizing four cases of flaccid blisters and skin peeling resembling scalding. In all cases, there was a prodromal syndrome of "toxemia." Histology demonstrated apoptosis of keratinocytes leading to epidermal detachment.[7] We now recognize that this is caused by apoptosis of the epidermal layer mediated by a type IV hypersensitivity reaction of cytotoxic T lymphocytes.[1,2] Further mechanisms of action are unknown. There are several theories that suggest a complex interaction of the drug with receptors to varying degrees leading to immunogenicity. Cytotoxic proteins isolated in the blister fluid such as granulsyn, Fas, and Fas ligand likely have a role in the apoptosis of keratinocytes.[1,4,8,9] Multiple recent studies suggest HLA association with a predisposition to SJS and TENS with exposure to certain drugs. This may be useful in certain academic institutions where testing for HLA subtypes are available prior to starting medications. One such association found in 2004 is with HLA-B*1502 and the Han Chinese, predisposing them to TENS and SJS after use of carbamazepine.[1,4] Other testing methods such as patch testing or in vitro studies are not as sensitive although considered safe

six months after recovery. It has been shown to be positive in as few as 24% of patients with SJS and TENS.[3, 4]

The most highly associated culprit drugs are allopurinol, antibiotics, nonsteroidal medications of the oxicam variety, and anti-seizure medications. Of antibiotics, sulfonamides and HIV antivirals are most commonly implicated. Of the anti-seizure medications, carbamazepine, phenobarbital, and phenytoin have previously been implicated. Of the newer generation medications, nevirapine and lamotrigine have had high associations due to increased usage.[10] Mycoplasma, disseminated candidiasis, CMV infection have also been known to cause SJS/TENS.[2,11] In up to 20% of patients, the cause is never identified. Exposure to such common drugs as acetaminophen and nonsteroidal anti-inflammatory agents have been implicated but in most studies, there was concomitant use of other drugs that was confounding, thereby making it difficult to identify the causative agent. The ALDEN score is a tool that has been used to identify the most likely culprit drug. This algorithm relies on multiple historical factors including timing of onset of symptoms and the presence of a "high-risk" drug, which is based on exposures in prior case control studies.[12]

The most vital step for management is determining and withholding the offending drug.[1,13] Prognosis is improved with earlier withdrawal of the culprit medication and if the medication has a shorter half-life. Otherwise, treatment is mainly supportive. Proper wound care must be performed to prevent sepsis.[2,4] Fluid resuscitation and early enteral feeding with nasogastric tube are also vital. Antibiotics are not indicated unless there is evidence of infection. Because of the severity of desquamation, patients usually require intensive care unit admission or transfer to a burn center for higher risk patients.[4]

More specific treatment strategies are still undergoing investigation. Supporting evidence for specific treatments have been limited to retrospective or non-randomized prospective studies. Low disease prevalence has made randomized control studies difficult to perform. There have been varied reports of success with corticosteroids, IVIG, cyclosporine, cyclophosphamide, and anti-TNF inhibitors. The controversy regarding corticosteroids revolves around whether they could benefit or cause harm. Specifically, use of corticosteroids could inhibit skin healing and increase susceptibility to infections. However, some observational studies described improvement of mortality particularly if steroids are limited to a pulse dose and tapered quickly.[2,11] The association of the FAS and FAS ligand to apoptosis in the epidermis have also led some to believe that IVIG would be beneficial. Again, there has been mixed evidence for its use with some finding an increased mortality or no significant benefit and others a reduced mortality. This may be due to the timing of IVIG administration and the dosage given.[8,9,14,15] Cyclosporine acts by inhibiting T cell lymphocyte mediated cytotoxicity and may be useful as observational studies show a trend toward benefit.[4] Only one randomized, double-blinded study has been done which evaluated thalidomide, a medication with anti-TNF alpha activity. This study was terminated early due to excess deaths in the thalidomide group. Published observational studies are promising but are insufficient to suggest a benefit in other anti-TNF alpha agents such as infliximab and etanercept.[4,15]

Prognosis varies with mortality ranging from 5% in SJS to 30% in TENS. The SCORTEN is a TEN specific score that can be used to identify those that have a higher risk of mortality. Independent predictors of death include initial percentage of detachment, age>40, delay in withdrawal of the culprit drug, presence of malignancy, and tachycardia above 120. Serum BUN, glucose, and bicarbonate also play a role in calculating the score.[13] Additionally, other factors such as chronic kidney disease, old age, and cardiovascular diseases may augment sensitivity of certain drugs like allopurinol. The most common sequelae are ocular and cutaneous scarring although bronchial and pulmonary scarring have also been noted.[1] Hyper and hypopigmentation are the most common findings along with severe dry eyes.[2]

This patient was diagnosed with SJS/TENS overlap based on histology demonstrating apoptosis of the epithelial layer. Timing of medication administration suggests that the most likely culprit medication was sulfamethoxazole. Fortunately, this patient was a healthy young female with a low SCORTEN score that did not require burn center transfer and she recovered well. This case demonstrates the need for better antibiotic stewardship. Given the severity of such drug reactions, physicians should consider whether antibiotics are really indicated before prescribing them.

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