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Abstract

Purpose: To report a probable association of Stevens-Johnson Syndrome (SJS) with furosemide and suspected cross-sensitivity with lincomycin and silver sulfadiazine cream. **Summary:** A 28-year-old Hispanic male was admitted for SJS, with a prolonged hospital course and unclear etiology throughout the majority of the stay. Patient's medications prior to development of SJS symptoms were stable for 3 months and with the exception of furosemide, all were continued throughout the hospitalization while the SJS resolved. During hospitalization, the patient was unintentionally rechallenged with furosemide, after which the rash reappeared and then worsened further with use of silver sulfadiazine cream. At this point in the hospitalization, the prolonged course of the rash prior to admission and the administration of lincomycin 3 days prior to admission were revealed. This suggests the SJS was initially caused by furosemide, a nonaromatic sulfonamide diuretic, with slow progression prior to hospital admission over approximately 7 weeks, followed by an acute worsening caused by lincomycin, a sulfide antibiotic. **Conclusion:** Use of the Naranjo ADR Probability Scale indicates a probable relationship between SJS and furosemide in this patient. Clinicians should be aware of this rare potential adverse effect, even months after the initiation of therapy.

Keywords

Stevens-Johnson Syndrome (SJS), furosemide, silver sulfadiazine

Introduction

Stevens-Johnson syndrome (SJS) is a relatively uncommon but potentially life-threatening cutaneous reaction that is most often drug-induced.¹ The reaction typically has a prodrome in which influenza-like symptoms (sore throat, fever, myalgia) precede the cutaneous reaction.¹ The cutaneous reaction begins as a papular rash and progresses to desquamation of skin. Mucosal erosions commonly occur and contribute to complications such as esophagitis, conjunctivitis, and pneumonitis. It is generally accepted in the medical community that SJS and toxic epidermal necrolysis (TEN) are on different spectrums of the same disease. The histopathologic findings for SJS and TEN are indistinguishable with full-thickness epidermal necrosis and detachment. If a patient has <10% epidermal detachment, the reaction is referred to as SJS, 10%-30% is considered SJS and TEN overlap, and >30% is TEN.¹ Mortality rates for SJS are typically less than 5% but increase to 30% in patients with TEN.

This case report describes a probable association of SJS with furosemide and suspected cross-sensitivity with lincomycin and silver sulfadiazine. Furosemide, a nonaromatic sulfonamide diuretic, has been reported as a possible cause of SJS.² Although furosemide was discontinued as the most likely cause in the previously published case, other concomitant medications and disease states were not completely ruled out. While

no conclusive report of SJS with furosemide have been published in the literature, other severe cutaneous reactions, including erythema multiforme and exfoliative dermatitis, have been well documented with furosemide use. In the cases reporting erythema multiforme, the reactions occurred from 4 days to 5 months after initiation of furosemide therapy.³⁻⁵ Stevens-Johnson syndrome, commonly iatrogenic, also has a very unpredictable timeline after initiation of the causative agent.⁶

Case Summary

A 28-year-old Hispanic male was admitted to the hospital with possible SJS. The patient's past medical history was significant for methamphetamine-induced cardiomyopathy and a negative test for human immunodeficiency virus (HIV) and herpes simplex virus (HSV). The patient was diagnosed with cardiomyopathy approximately 4½ months prior to this hospitalization.

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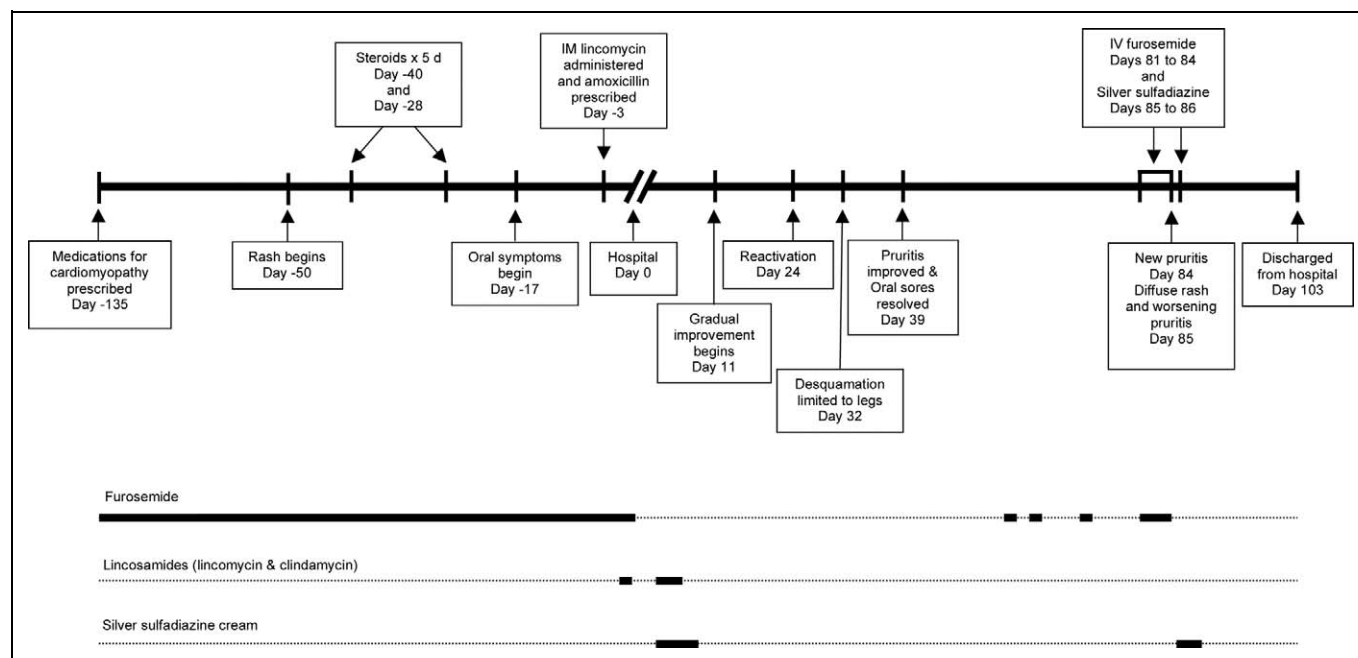


Figure 1. Timeline.

Since diagnosis, the patient was reportedly compliant with his heart failure regimen of furosemide 40 mg daily, enalapril, metoprolol succinate, spironolactone, and digoxin.

The course of this patient's SJS was complicated by a slow development over approximately 7 weeks and an acute worsening over 3 days (see Figure 1). The first objective evidence of the patient's rash was documented at a previous hospital visit 50 days prior to the current hospital admission. Clinic visits 40, 28, and 17 days prior to current admission document a red, itching, papular skin rash on his chest and arms. Following the clinic visits on days 40 and 28 prior to current admission, the rash was somewhat relieved by 5-day courses of corticosteroids but never completely resolved and gradually worsened. Additionally, oral involvement was documented 17 days prior to hospitalization as white spots on his tongue with no fever. These progressed to oral blisters, which reportedly ruptured and healed, 4 or 5 days prior to hospitalization.

During a clinic visit for the rash and sore throat 3 days prior to the current hospital admission, the patient was treated empirically for pharyngitis with an intramuscular injection of lincomycin, a prescription for a 10-day course of oral amoxicillin, and acetaminophen. The patient stated his rash worsened "all of a sudden" following this clinic visit. Three days later, he presented to the emergency department with peeling, blistering skin, painful oral blisters, and oral ulceration, from which pain prevented him from eating. Upon arrival, the patient's vital signs were as follows: blood pressure: 98/70 mm Hg; heart rate: 140 beats per minute; respiratory rate: 20 breaths per minute, and temperature: 37.8 degrees Celsius.

In the emergency department, the patient reported a history of a rash, but nothing similar to what he experienced over the past 3 days. The dermatology exam showed dusky, generalized

erythema of skin with palmoplantar scaling, as well as conjunctival and oral mucosal ulceration. Blisters covered the patient's neck and face. The syndrome affected approximately 75% of the patient's body, and sloughing of skin affected 5%-10% of the patient's body. A punch biopsy of the patient's skin showed marked keratinocyte necrosis of the epidermis with denuded epithelium and adjacent basal vacuolopathy, which was reported to be consistent with SJS. Histology of the punch biopsy in addition to oral and conjunctival mucosa involvement were consistent with SJS.

The patient had a prolonged hospital course due to infectious and thrombotic complications, as well as acute renal failure that eventually resolved. The likely etiology of the SJS was unclear throughout the majority of his stay. On admission to the hospital, amoxicillin was discontinued as it was suspected to be the cause of the SJS due to the patient reporting his current symptoms began following initiation of amoxicillin; furosemide and enalapril were also discontinued at this time. The patient was treated with diphenhydramine, topical corticosteroids, and silver sulfadiazine, a sulfonamide antimicrobial cream, for his symptoms. On hospital days 2 and 3, the patient received intravenous (IV) clindamycin, levofloxacin, and vancomycin as empiric treatment for a suspected bloodstream infection. The patient only experienced slight improvement until systemic corticosteroids were initiated on hospital day 4, which did alleviate the patient's itching but were discontinued on day 6 due to bacteremia. The silver sulfadiazine cream was discontinued on hospital day 9 and topical corticosteroids were continued for approximately 6 weeks. It was not until hospital day 11 when his reaction began marked improvement. On hospital day 24, the reaction worsened with increased rash affecting the entire body and recurrence of skin desquamation.

Because at the time no suspected medications correlated with both the worsening and improvement in his symptoms, this worsening of his condition was considered a reactivation of the initial reaction. The reaction again improved with desquamation limited to his legs by day 32, itching improved around day 36, and oral sores resolved by day 39. Despite improvement in the rash, mild pruritus continued the remainder of the hospital stay. The patient maintained a euvolemic status throughout most of the hospital stay but did receive intermittent furosemide therapy on 3 occasions: 20 mg orally (PO) on day 65 and 40 mg IV on day 66; 20 mg IV on day 76; and 80 mg IV on day 81 followed by 40 mg IV every 8 hours on days 82 through 84 (see Figure). On hospital day 84, the patient complained of new itching. A diffuse rash appeared on hospital day 85 on both hands and palms, with generalized pruritus. Subsequently, he was treated with systemic diphenhydramine and topical silver sulfadiazine. The patient used a large amount of this cream over 2 days, which resulted in worsening pruritus (see Figure 1). The silver sulfadiazine cream was discontinued on day 86, and his pruritus began to improve on day 88. The patient reported his itching was significantly improved by day 94 and only minimal pruritus was reported at his discharge on day 103.

As mentioned, upon admission the SJS was suspected to have been caused by the amoxicillin. However, on hospital days 25 through 58, the patient received imipenem/cilastatin for *Acinetobacter baumannii* bacteremia with susceptibility only to imipenem, and he experienced no worsening of his initial reaction. This suggested that the cause of SJS in this patient was not the beta-lactam antibiotic amoxicillin. Following the observation of increased symptoms with the silver sulfadiazine cream, the patient's previous medical records were reviewed in detail, which revealed the prolonged course of the rash prior to admission and revealed the administration of lincomycin, a sulfide antibiotic, at the time of initiation of amoxicillin. At this point in the hospital course, the patient's medications were reviewed in detail for correlation of sulfa-containing medications with SJS symptoms. A temporal relationship was discovered between the reactivation of SJS symptoms on hospital day 84 and scheduled administration of IV furosemide every 8 hours on hospital days 82 through 84. This suggests the SJS was initially caused by furosemide, a nonaromatic sulfonamide diuretic, with slow progression over approximately 7 weeks, followed by an acute worsening caused by lincomycin, a sulfide antibiotic.

Discussion

Despite the complicated history and multiple medications the patient was taking prior to the development of SJS, using the Naranjo Adverse Drug Reaction Probability Scale, furosemide was assigned a probable etiology score (6 points) in this patient.⁷

First, in assessing furosemide, there has been one published case report documenting SJS with furosemide use, however, the authors did not determine the case to be conclusive.² Next, the temporal relationship of SJS symptoms was correlated with furosemide use because SJS occurred after the initiation of

furosemide therapy and the reaction resolved after it was discontinued. In this case, SJS symptoms first appeared after 3 months of furosemide therapy and slowly progressed over 7 weeks, which supports the unpredictable timeline of SJS. Furthermore, a positive rechallenge was indicated by the administration of furosemide on hospital days 82 through 84, with increased rash, pruritus, flaking, and possible reactivation of SJS on day 84. However, there was no reactivation of SJS symptoms when the patient received small intermittent oral doses of furosemide on hospital days 65, 66, and 76. This may suggest a dose-response relationship, which could also be supported by the less severe reactivation symptoms following 2 days of furosemide therapy compared to the more severe initial reaction following months of daily furosemide therapy. No placebo was given to determine if the reaction reappeared upon administration, and the drug levels of furosemide were not checked as toxic levels in biological fluids are not established for furosemide.³

SJS in this patient was objectively confirmed by histology and clinical findings. Other alternative causes of SJS include medical conditions, as well as medications. However, this patient tested negative for both HIV and HSV, which ruled these conditions out as possible causes of SJS. Sulfonamide and beta-lactam antibiotics are the most common medications reported to cause SJS. While this patient was never administered a systemic sulfonamide antibiotic, the use of topical silver sulfadiazine and scheduled IV furosemide on hospital days 82 through 84 did appear to reactivate SJS in this patient. This may represent an additive effect and cross-sensitivity of sulfonamide components in his reaction. While cross-sensitivity of a non-antibiotic sulfonamide in a patient allergic to a sulfonamide antibiotic is of concern, this cross-sensitivity of allergic reactions between sulfonamide antibiotics and sulfonamide non-antibiotics appears to be low.⁸ Furthermore, a cross-sensitivity between sulfonamide and lincosamide antibiotics has not been established in the literature. In this patient, the SJS reaction increased in severity rapidly after administration of lincomycin, which is reported to be associated with SJS.⁹ Since lincomycin is a sulfide antibiotic, it cannot be ruled out that the patient progressed to SJS due to additive effects of the sulfonamide furosemide and sulfide lincomycin. In this patient, the common underlying trigger is unclear, but a similar reaction to systemic sulfonamide antibiotics in this patient cannot be excluded. It is interesting to note the relatively slow progression of rash to SJS although this could be due to variable compliance to furosemide during the outpatient period preceding admission to the hospital. Regarding beta-lactam antibiotics, the temporal relationship of amoxicillin therapy prior to hospitalization was initially reason to consider this as a cause. Though the carbapenem class has up to a 25% cross-sensitivity with the penicillin class,¹⁰ it was necessary to treat this patient with imipenem/cilastatin. Since the patient tolerated imipenem while his SJS symptoms continued to improve, it was thought that amoxicillin was not the cause of SJS. Additionally, the patient experienced reactivation of the reaction when beta-lactam antibiotics were not being administered. Prior to the initial reaction, the patient was taking a number

of other medications that could have been the culprit for SJS. These include pantoprazole, digoxin, spironolactone, and enalapril.¹¹⁻¹⁴ However, his cutaneous reaction improved and resolved while taking these medications daily in the hospital.

Conclusion

Use of the Naranjo ADR Probability Scale indicated a probable relationship between SJS and furosemide therapy in this patient.⁷ SJS and erythema multiforme have been reported with furosemide use, and sulfonamides are the most common cause of SJS. Also, the potential for additive effects should be considered when using sulfa-containing products. In this case, the role played by lincomycin and silver sulfadiazine cream, (a sulfide and sulfonamide derivative, respectively) is unclear. This case represents only the second reported case of furosemide-associated SJS in the literature. Clinicians should be aware of this potentially rare adverse effect of SJS with furosemide, even months after the initiation of therapy.

Declaration of Conflicting Interests

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