

## A New-Onset Rash in the Setting of Rifaximin Treatment for Hepatic Encephalopathy

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### Abstract

We present one of the first cases in the literature to describe an association between Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and rifaximin treatment in a patient with a recent diagnosis of alcoholic hepatitis, stage 2 hepatic encephalopathy, and no known existing allergies. Although SJS/TEN may be a rare reaction with rifaximin, it should be an important clinical consideration.

### Introduction

Hepatic encephalopathy (HE) results when the systemic circulation is overwhelmed by gut-derived neurotoxins, particularly ammonia, in patients with impaired liver function.<sup>1</sup> Standard-of-care therapy consists of identifying precipitating factors, providing supportive care, and increasing fecal excretion of ammonia with the use of a non-absorbable disaccharide such as lactulose.<sup>2</sup> Antibiotics such as rifaximin may also be used to decrease the number of ammonia-producing bacteria in the gastrointestinal tract for the treatment and secondary prevention of HE.<sup>3</sup> Rifaximin, a gut-selective antibiotic, is a desirable treatment option as it has side effects similar to placebo.<sup>1</sup> To date, the association between rifaximin and the development of toxic epidermal necrolysis (TEN) has only been reported once.<sup>4</sup>

### Case Report

A 42-year-old female with no known allergies and a past medical history significant for alcoholism and obesity (BMI 32 kg/m<sup>2</sup>) status-post Roux-en-Y gastric bypass presented with 4 weeks of nausea, yellowing skin, dark urine, light-colored stools, and a 16-kg weight loss. She was diagnosed with alcoholic hepatitis complicated by hepatic encephalopathy (HE). Treatment medications included spironolactone, furosemide, folic acid, ferrous sulfate, and lactulose. The patient was drowsy but arousable. Physical exam showed sinus tachycardia, scleral icterus, asterixis, jaundice, lower extremity edema, and stage 2 encephalopathy. She was treated with lactulose, spironolactone, rifaximin 550 mg orally twice daily, and zinc. The patient remained tachycardic, thought to be secondary to diuresis and increased stool output; spironolactone and lactulose were discontinued. Subsequently, her vital signs normalized and mental status cleared. She was discharged to home with instructions to restart the spironolactone and continue the rifaximin 550 mg orally twice daily, as well as the zinc, thiamine, folic acid, and ferrous sulfate. The patient was also instructed to not restart furosemide and lactulose due to continued hypokalemia and excessive number of bowel movements.

*ACG Case Rep J* 2014;2(1):42–44. doi:10.14309/crj.2014.79. Published online: October 10, 2014.

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**Figure 1.** Diffuse erythematous, papular, bullous rash on the elbows and feet.

Two days after discharge, the patient returned to our emergency department for evaluation of confusion, fatigue, anorexia, nausea, pruritus in the setting of a new tremor, oral mucosal ulcerations, and diffuse rash. She denied any other recent illness or sick contacts since discharge. She endorsed compliance with the prescribed discharge medications, including rifaximin. She denied use of any new medications, supplements, or foods. On physical exam, the patient was afebrile, tachycardic, and normotensive. She had facial angioedema, scleral icterus, and a diffuse erythematous, papular, bullous rash (Figure 1) with associated ulcerations of her oral and vaginal mucous membranes, and a positive Nikolsky sign. Her abdomen was non-tender with mild-to-moderate ascites. A bilateral tremor and stage 1 encephalopathy without overt asterixis were noted. Due to concern for an allergic reaction to either rifaximin or spironolactone, both medications were discontinued and the patient was admitted to the burn unit.

A representative bullous lesion was biopsied showing epidermal necrosis consistent with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Skin involvement and mucosal ulcerations progressed to include 10–30% of her total body surface area. The patient was monitored in the burn unit for 17 days until the SJS/TEN lesions resolved.

Although the patient's SJS/TEN course was improving, she developed fever and hypotension secondary to her underlying liver disease and died on hospital day 48.

## Discussion

SJS/TEN is a medical emergency and can be life-threatening.<sup>5</sup> It represents a disease spectrum that differs by the amount of body surface area affected: SJS is less than 10%, while TEN is greater than 30%.<sup>5</sup> For patients between 10–30%, the disease is described as a SJS/TEN overlap.<sup>5</sup>

Classically, SJS/TEN begins with prodromal symptoms including generalized weakness, nausea, headache, fever, myalgias, and/or diarrhea that may last for 1–14 days before the acute-onset rash.<sup>5</sup> Our patient did endorse generalized weakness, nausea, and fatigue starting about 5 days prior to presentation of the rash. However, given her history and the absence of any skin findings, her symptoms were attributed to the alcoholic hepatitis complicated by hepatic encephalopathy, for which rifaximin was prescribed.

Spironolactone was also considered as a possible cause; however, this was less likely due 3 factors: 1) the spironolactone was initiated 29 days prior to presentation, 2) the dose of spironolactone was doubled without any skin manifestations, and 3) the spironolactone was held for the majority of the prior admission. Although it is possible to see a delayed reaction, case-control studies have found that the risk for SJS/TEN is greatly reduced after the first weeks of drug administration.<sup>5</sup>

Rifaximin, a rifamycin derivative, has been associated with SJS/TEN in a prior case study.<sup>4</sup> Furthermore, the development of SJS/TEN due to rifampin, another rifamycin derivative, has been reported in the literature.<sup>6,7</sup> Rifaximin was believed to be the causative drug due to the close temporal relationship between its initial administration and SJS/TEN development. An extensive medication review and application of the Naranjo scale—a method to estimate the probability of a particular drug causing an adverse drug reaction with a high specificity—supports rifaximin as the likely culprit.<sup>8,9</sup> Although rifaximin is considered to be a non-absorbable drug, we hypothesize that rifaximin or its metabolites are absorbed by a mechanism that allows a cytotoxic immune reaction to occur.<sup>10</sup> Prior studies have demonstrated that certain patients have a decreased ability to detoxify reactive metabolites, especially in the setting of underlying liver disease.<sup>11,12</sup>

Rifaximin as the causative agent of SJS/TEN is a rare but serious complication. Early recognition and immediate cessation of any potential causative agents, such as rifaximin, is imperative.

## Disclosures

Author contributions: CDL Fritz and C. Adebajo drafted the manuscript. A. Aronsohn drafted and critically revised the manuscript for important intellectual content, and is the article guarantor. DM Jensen critically revised the manuscript for important intellectual content.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received: June 2, 2014; Accepted: July 27, 2014

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