Rifaximin induced Stevens–Johnson syndrome in a patient of acute on chronic liver failure

Abstract

Stevens–Johnson Syndrome (SJS) forms part of a spectrum of severe adverse cutaneous reactions that can eventually culminate into toxic epidermal necrolysis (TEN), a potentially fatal condition. Drugs, most commonly allopurinol, antivirals, antiepileptics, sulfonamides and other antibiotics are implicated in this disease, even though, many case reports and series describe a variety of associations with many other classes of drugs. Infectious and inflammatory conditions also predispose to this severe cutaneous disease. Here, we present a patient who was initially diagnosed as a case of acute on chronic liver failure in hepatic encephalopathy grade I, in whom the introduction of rifaximin therapy led to aggressive cutaneous reactions, leading to SJS, which was managed with intensive supportive treatment because of which the patient improved substantially and was discharged after 14 days of onset of a potentially fatal condition. Rifaximin therapy leading to SJS-TEN has been reported only once before.

Key words: Acute on chronic liver failure, cirrhosis, drug reaction, hepatic encephalopathy, rifaximin, Stevens–Johnson syndrome, toxic epidermal necrolysis

INTRODUCTION

Stevens–Johnson Syndrome (SJS) consists of a spectrum of severe cutaneous adverse reactions affecting the skin and mucous membranes. It is the initiating part that culminates into severe toxic epidermal necrolysis (TEN). SJS was initially considered to resemble erythema multiforme with mucosal involvement but is now thought to form a single disease entity.[1] It is less severe than TEN, but the etiology, genetic susceptibility, and pathological mechanisms are same for SJS-TEN. In 1993, a consensus definition[2] for differentiating these overlapping conditions was proposed by Bastuji-Garin et al. Accordingly, classification into five categories were proposed – bullous erythema multiforme, SJS, overlap SJS – TEN, TEN with spots and TEN without spots. SJS is named after the 1922 description by Stevens and Johnson. Most authors give credit for the first description of SJS to Hebra in 1860,[3] but there is a mention in an 1822 publication by Alibert and Bazin[4] that probably refers to the same disease. SJS and TEN differ only by their extent of skin detachment. The condition is mainly caused by drugs, but infective etiology and other unknown risk factors in the presence of susceptibility play a role in its development. Identification of the cause is of utmost importance because in the presence of drug-induced SJS and withdrawing the offending agent almost always yield good results. A variety of drugs are found to be associated with SJS and TEN. In SJS and TEN the distribution of gender is almost equal (slightly more females) and a female preponderance of approximately 65% is seen in SJS/TEN-overlap, whereas more men or boys develop erythema multiforme majus (almost 70%). The mortality is almost 10% for patients with SJS, approximately 30% for patients with SJS/TEN-overlap and almost 50% for patients with TEN. The onset of the reaction, age of the patient, underlying diseases and the amount of skin detachment are factors associated with mortality in SJS-TEN. In contrast, no patient with erythema multiforme majus dies as a consequence of the disease state.[5] Large studies have shown that the highest risk for short-term drug-induced SJS was documented with trimethoprim-sulfamethoxazole and other sulfonamide antibiotics. Other reported associations with SJS/TEN include infectious diseases such as those caused by human immunodeficiency virus, herpesvirus, mycoplasma pneumoniae and hepatitis A virus and noninfectious conditions such as radiotherapy, lupus erythematosus and collagen vascular disease.[6] Genetic factors associated with SJS-TEN include human leukocyte antigen (HLA)-B12 phenotype and the HLA-B*5801 and
HLA-B*1502. The risk of carbamazepine-induced SJS/TEN was significantly higher in patients with HLA-B*1502 in Indian patients.\(^7\) The median latency time between the beginning of use and onset of SJS/TEN (also called index-day) is usually <4 weeks for most drugs whereas it was much longer for drugs with no associated risk.

Acute on chronic liver failure (ACLF) is characterized by the acute deterioration of liver function in a patient with known/unknown underlying compensated. The Asian Pacific Association of Study of Liver in 2009 defined ACLF as an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.\(^8\) Even though SJS and TEN have been reported numerous times in the presence of variable etiologies, mostly drugs, its presence in a patient of ACLF that was induced by rifaximin intake is a novel presentation and arguably the second case to be reported on rifaximin and the first, in the presence of ACLF.

**CASE REPORT**

A 38-years-old alcohol consumed patient with a recent intake 14 days back presented to our out-patient department with complaints of worsening anorexia and lethargy associated with progressive noncholestatic jaundice and painless abdominal distension since a period of 3 weeks. The patient denied comorbid illnesses and has not been on any medications otherwise, including complementary and alternative therapy. The patient denied prior allergies or hypersensitivity reactions. On examination, the patient was conscious and oriented with poor alertness without asterixis and was hemodynamically stable. Pallor was evident as was icterus; there were no clubbing, peripheral lymphadenopathy; and mild bilateral nontender pedal pitting edema was present. The abdominal examination revealed firm hepatosplenomegaly in the presence of grade 2 ascites. The rest of the systemic examination was essentially normal. Laboratory investigations revealed the presence of anemia, thrombocytopenia with normal peripheral leucocyte counts of 12,000 cells/cumm. There was macrocytic anemia on peripheral smear and infection such as serum procalcitonin and baseline cultures were all negative. Liver function tests showed marked abnormality with total bilirubin of 8.4 mg/dL with a direct fraction of 5.43 mg/dL, hypoalbuminemia, aspartate aminotransferase of 220 IU/dL and alanine aminotransferase of 80 IU/dL. The prothrombin time was 16.8 s (control 12.0 s) with an international normalized ratio of 2.24 and a discriminant function of 30.5. The kidney function tests were normal. The markers of hepatotropic viruses and retroviral assays were negative. The imaging findings were suggestive of cirrhosis with portal hypertension with moderate ascites. A diagnosis of ACLF with acute insult being alcoholic hepatitis and chronic being alcoholic cirrhosis was made. The patient was started on nutritional measures with protein rich, high-calorie diet and lactulose for adequate purging. Rifaximin at the dose of 400 mg every 8th hourly was started and antibiotics were held in the absence of overt sepsis or infection. Sixteen hour after start of rifaximin therapy, the patient complained of feeling of impending doom and restlessness. This was followed by eruptions of diffuse maculopapular erythematous lesions, which started on the face and upper chest which then spread aggressively to the other parts of the body, most prominent on the anterior chest, abdomen and at the back with subsequent involvement of both eyes [Figure 1]. Later on, oral and mucosal involvement commenced and desquamation of the skin over the body began to appear. The patient became febrile and toxic subsequently and a suspected diagnosis of a severe cutaneous adverse drug reaction, possibly SJS was made. Using the Naranjo Scale (Naranjo, Busto, Sellers et al. [1981]), rifaximin as a possible cause of the drug reaction was determined. Subsequently, rifaximin was discontinued and antihistamines, aggressive hydration measures along with tapering doses of corticosteroid therapy was initiated. The patient was shifted to a high dependency unit and adequate skin antisepsic measures, daily dressings over the desquamated and peeled skin areas, hydration, nutritional supplementation and broad spectrum antibiotics (Cephalosporins, 4th generation) were continued. The patient slowly but steadily improved within 6 days of stopping the offending drug and supportive measures with resolution and healing of skin and oral and mucosal lesions. He was subsequently discharged 2½ weeks after initial admission to the hospital.

**DISCUSSION**

The initial symptoms of SJS-TEN are nonspecific and include symptoms such as fever, stinging eyes and discomfort upon
swallowing with loss of general well-being. These symptoms precede cutaneous manifestations by a few days typically. Early on in the disease, common sites of cutaneous involvement include prester nal region of the trunk and the face, and also the palms and soles. Involvement (erythema and erosions) of the buccal, genital, and/or ocular mucosa occurs in >90% of patients. Ocular involvement is frequent, and present variably, including acute conjunctivitis, eyelid edema, erythema, crusts, and ocular discharge, to conjunctival membrane or pseudomembrane formation or corneal erosion, cicatrizing lesions, symblepharon, fornix foreshortening and corneal ulceration. In our patient, there was early involvement of eyes with diffuse cutaneous lesions typical of SJS with not >10% of body surface involvement. A second phase of this disease is characterized by large areas of epidermal denudation. In the absence of denudation, exerting tangential mechanical pressure on several erythematous zones (Nikolsky sign) can produce desquamation (but is not specific for TEN or SJS). Even though histological examination including direct immunofluorescence analysis of affected skin biopsy specimens is important to rule out differential diagnoses such as autoimmune blistering diseases, bullous fixed drug eruption, and acute generalized exanthematous pustulosis, this was not done in this case in view of underlying coagulopathy and also in the wake of strong clinical diagnosis of SJS. The extent of skin involvement is a major prognostic factor. Necrotic skin, which is already detached or detachable skin, should only be included in the evaluation of the extent of skin involvement. Drug exposure and resulting hypersensitivity reaction [Table 1] is the cause of a large majority of cases of SJS/TEN. Allopurinol was the most common cause of SJS/TEN in studies done in Europe and Israel. The highest risk of induction of SJS-TEN was found to be more during the first 2 months of treatment. Interestingly, the long-term use of glucocorticosteroids for a variety of diseases does not change the incidence of the occurrence of SJS-TEN for the incriminated drugs, but it does lengthen the interval between the beginning of the intake of the drug and onset of SJS-TEN. Photo-induced TEN or SJS are only reported in very rare cases. The occurrence of SJS-TEN with use of rifaximin has been reported only once before. Our case represents the continuum of that report which proves that SJS-TEN occurrence can be associated even with the least suspected medication, such as rifaximin that is widely used in most patient of decompensated cirrhosis for treatment of hepatic encephalopathy and hepatopulmonary syndrome. Recently, a severity of illness score for TEN was published, which combined seven independent risk factors for mortality (age ≥ 40, heart rate ≥ 120/min, history of cancer or hematologic malignancies, involved body surface area > 10%, serum urea level > 10 mmol/L, serum bicarbonate level < 20 mmol/L and serum glucose level > 14 mmol/L). Scoring one point for each item, the predicted mortality was 3.2%, 12.1%, 5.3%, 58.3%, and 90.0% for 0–1, 2, 3, 4, and ≥ 5 points respectively. An energy intake of 120% of the predicted basal metabolic rate and intake of 3 g/kg protein result in adequate wound healing as shown by expert studies. The negative prognostic factors for mortality in SJS-TEN include the hypernatremia, increased blood urea nitrogen (BUN), neutropenia, thrombocytopenia, visceral involvement, and delayed presentation. Our patient had a raised BUN after the start of cutaneous illness and thrombocytopenia was evident even at admission in the presence of ACLF. In the presence of severe TEN with impending organ failures, the use of intravenous immunoglobulins or corticosteroids is advocated even though large studies failed to show any improvement in mortality as compared to supportive measures only. In our patient, the presence of SJS that did not progress to TEN was a sign of wellness and eventual recovery with aggressive management even in the presence of a serious illness such as ACLF was seen. The importance of management of SJS or TEN in the wake of ACLF is to prevent organ failures. Timely therapeutic intervention, quick diagnosis and immediate removal of the offending agent resulted in the patient not having unwanted events during the hospital stay. Severe cutaneous adverse reactions in liver disease patients, in the presence of a widely used drug like rifaximin is a remote possibility, which when tackled well, can lead to life salvage.

**REFERENCES**


Philips, et al.: Rifaximin induced SJS in ACLF


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