Adefovir-induced Stevens-Johnson syndrome and toxic epidermal necrolysis overlap syndrome

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ABSTRACT

An increasing number of patients with chronic hepatitis B infection are being treated with the newly licensed drug, adefovir. It is an acyclic nucleoside phosphonate that is relatively safe in the dosage generally used for chronic hepatitis B. Serious adverse cutaneous drug reactions like Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) following adefovir use have not been reported. We report a case of adefovir-induced SJS and TEN overlap syndrome in a patient with chronic hepatitis B infection.

Keywords: adefovir, adverse drug reaction, Stevens-Johnson syndrome, toxic epidermal necrolysis

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INTRODUCTION

Adefovir dipivoxil (ADV), a highly orally bioavailable prodrug form of adefovir, which is an acyclic nucleoside phosphonate, selectively inhibits hepatitis B virus (HBV) deoxyribonucleic acid (DNA) polymerase with its active intracellular metabolite adefovir diphosphate. This prodrug has recently been licensed for the treatment of HBV. As an acyclic nucleoside phosphonate, adefovir does not depend on virus-induced kinases to exert their antiviral action, and also acts against a broad range of DNA viruses, including retroviruses such as human immunodeficiency virus (HIV), hepadnaviruses, as well as herpes viruses by "bypassing" the nucleoside kinase step.[1] In addition, adefovir is active against wild-type HBV infection, HIV and HBV co-infections, and in lamivudine-resistant HBV and precore mutant (e antigen-negative) HBV patients.[2-5] At a dose of 10 mg/day, ADV is well tolerated in some patients, with no significant nephrotoxicity or side effects except for a transient increase in alanine aminotransferase (ALT) levels and a better risk-benefit ratio on long-term treatment.[2,6] We report a case of adefovir-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) overlap that developed following the administration of adefovir in a patient suffering from chronic hepatitis B infection. To the best of our knowledge, SJS or TEN due to adefovir has not been reported in the literature.

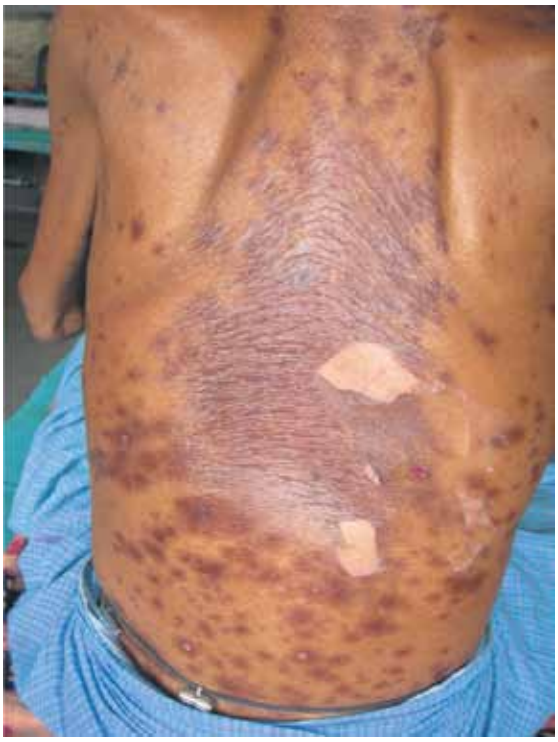

Fig. 1 Clinical photograph shows widespread dark patches on the back of the trunk with many areas of complete detachment of skin.

CASE REPORT

A 59-year-old non-smoker, non-drinker male patient suffering from chronic HBV for the last seven months consulted a hepatologist for antiviral therapy. Investigations revealed that he was positive for hepatitis B surface antigen and hepatitis B e-antigen (HbeAg). The patient's viral load for HBV DNA was 3×10^7 copies/ml and the ALT level was 187 IU/L. He had been on oral lactulose, ursodeoxycholic acid, propranolol and spironolactone for the past five months. In February 2009, he was prescribed a new treatment regime containing an additional daily dose of ADV 10 mg. On Day 25 of ADV therapy, he developed fever, chills, malaise, headache and nausea, which progressed over the next two days

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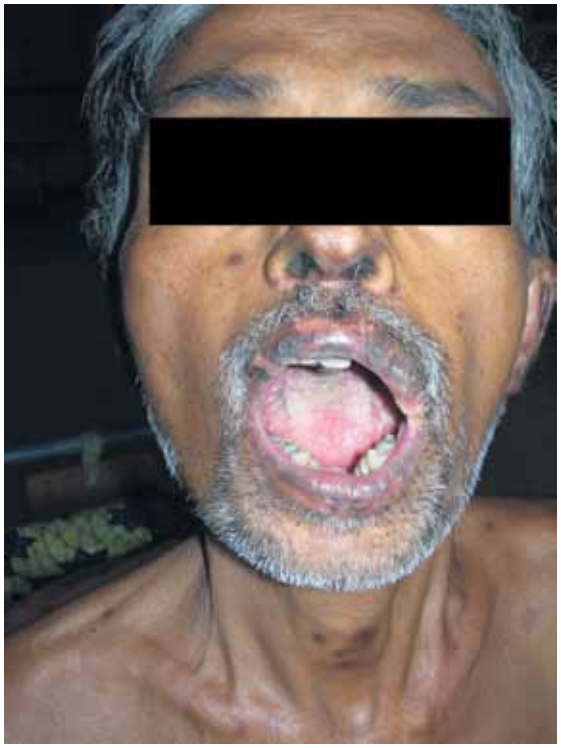

Fig. 2 Clinical photograph shows crusted lesions over the lips following exposure to adefovir.

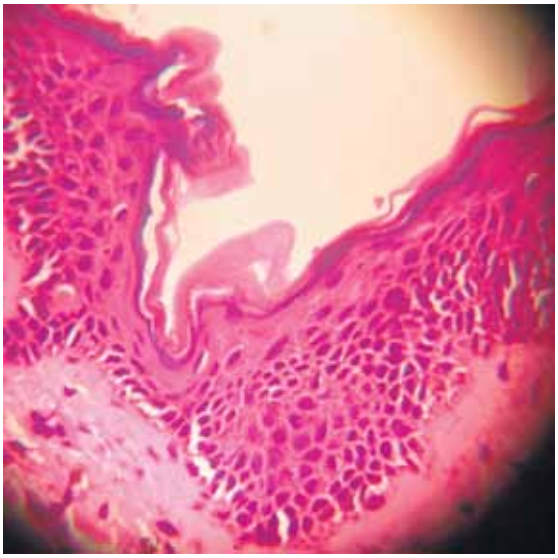

Fig. 3 Photomicrograph of the skin section shows mild hyperkeratosis, unremarkable epidermis and prominent basal cell degeneration, with minimal inflammatory changes (Haematoxylin & eosin, × 400).

with the appearance of a rash over the skin and mucosa. The patient was admitted to our institution on Day 28.

The patient was conscious and coherent on admission. Flapping tremour was absent, but he was mildly jaundiced and pale. Supine blood pressure was 116/74 mmHg and pulse was 88 beats/min. Multiple erythematous dusky maculae and several papules were found widespread over the patient's trunk, back, upper extremities, pinna and thighs, with some over the lower limbs. His face was spared except for pinna involvement. Flaccid vesiculation was noted in the central part of numerous lesions. The lesions merged to form a larger patch, with prominent denudation (Fig. 1) in the abdomen and at the centre of the back, with total involvement of less than 30% of the body surface area. The patient also had widespread mucosal involvement (ocular, oral and genital) with haemorrhagic crusts on the lips (Fig. 2).

An examination revealed that the dusky patches were very loosely attached to the skin and were easily detached with slight rubbing. Nikolsky's sign was positive on the normal skin near the lesions. A firm hepatomegaly measuring 14 cm with mild splenomegaly, moderate ascites and prominent superficial anterior abdominal veins was evident during abdominal examination. The cardiovascular system was within normal limits but there was minimal right-sided pleural effusion. Clinical examination of the nervous system did not reveal any cranial nerve involvement or long-tract signs. A clinical diagnosis of SJS-TEN overlap syndrome was made, and ADV was stopped, as it was the only new medication that was started in the last two months.

Pending laboratory work-up, the patient's skin lesions were managed symptomatically with antihistamines, wet dressing and temperature control by the use of soft warm blankets and electrolyte monitoring every three days till the lesions subsided. To prevent secondary infection, the treatments were performed in a sterile environment, such as the burns ward, and without using any oral or topical medicine. Proper nutrition was maintained through an oral feeding regimen. The patient was managed with ophthalmologic consultations, frequent instillation of tear supplements and a protective eye pad during sleep.

Laboratory tests revealed haemoglobin 9.7 gm/dL, total leucocyte count 6.9 × 10^3/μL (N65 L30 E2 M3), platelet count 1.7 × 10^5/μL, erythrocyte sedimentation rate 30 mm/hr (Westergren), total bilirubin 1.6 mg/dL (direct 0.6 mg/dL), ALT 96 IU/L, aspartate transaminase 51 IU/L, alkaline phosphatase 313 IU/L, serum albumin 2.5 gm/dL, urea 32 mg/dL, creatinine 0.9 mg/dL and HBV DNA load 9 × 10^6 copies/ml. Prothrombin time was prolonged by four seconds over control. HbeAg was positive, but anti-HBs antibody, anti-HBe antibody, anti-hepatitis C virus (HCV) antibody, HCV ribonucleic acid (RNA) and HIV I & II by ELISA were negative. Skin biopsy taken from a non-bullous lesion from the patient's back revealed mild hyperkeratosis, a normal spinous cell layer with basal cell degeneration and an unremarkable dermis with minimal inflammation (Fig. 3). Direct immunofluorescence of the skin biopsy taken

from the normal skin in a covered part of the thigh was negative. Based on clinical and histological findings, the case was diagnosed as SJS-TEN overlap syndrome most likely due to ADV. The patient's condition improved after stopping the use of adefovir; his fever subsided and the rash started to resolve in a week.

After careful consideration of all the drugs that were used in the patient, we found that adefovir was the most likely agent to have precipitated the dermatological reaction. Apart from ADV, the other drugs that were taken regularly or occasionally before and after the cutaneous drug reaction occurred did not cause any flare up. On the contrary, the patient recovered, lending credence to the hypothesis that ADV was the possible culprit. A final diagnosis of SJS-TEN overlap due to ADV was made. The patient was then discharged in a stable condition, with advice to follow up.

DISCUSSION

Adefovir is activated *in vivo* to a diphosphate metabolite which is incorporated into viral DNA, leading to selective viral RNA-dependent polymerase inhibition at concentrations almost 1 $\log_{10}$ lower than that required for inhibition of human RNA polymerase, DNA chain termination and impaired viral replication.[8] In addition, adefovir inhibits reverse transcriptase of hepatitis B, herpes and HIV,[9-11] induces natural killer cell activity and stimulates endogenous interferon production. As such, viral resistance develops at a slower rate.

The known side effects of adefovir are lactic acidosis, severe hepatomegaly with steatosis and renal toxicity on chronic use at a dose higher than 10 mg/day. Neurological, gastrointestinal, metabolic and dermatological manifestations are much less common. Antiretroviral hypersensitivity reactions, including the severe forms are unpredictable as the pathogeneses are largely unknown. The role of immune-mediated injury with the possible role of $CD4^+$ T cells, pro-inflammatory cytokines, altered drug metabolism with glutathione deficiency, slow acetylator status, duration and dose of therapy, and cytomegalo virus and Epstein-Barr virus co-infection have been postulated.[12] Severe adverse cutaneous drug reactions, such as SJS or TEN, are usually life-threatening and require urgent withdrawal of the drug. Mortality in cases of TEN may reach up to 34%.[13]

SJS, SJS-TEN overlap or TEN is diagnosed according to the degree of denudation, which ranges from <10%, 10%–30% and >30%, respectively. However, the surface area is not the only criterion, as TEN can only involve about 10% of the body surface area, with large sheets of epidermal detachability.[14] Severe drug-specific skin rashes like SJS are commonly reported with nevirapine, efavirenz and amprenavir use.[15] Hypersensitivity skin reactions also commonly occur with abacavir.[15] Although skin rashes have been reported after adefovir use,[16] patterns of the rashes are not characterised. Moreover, the control group in the study had nearly as many patients with skin rashes.[16] Life-threatening drug reactions like TEN or SJS have never been reported following adefovir. We have reported a case of SJS-TEN overlap after the use of oral ADV in a patient with chronic active HBV. To the best of our knowledge, this is the first report of ADV-induced SJS-TEN overlap.

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