Toxic Epidermal Necrolysis Associated with Sorafenib and Tosufloxacin in a Patient with Hepatocellular Carcinoma

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This is the first case report to describe a 44-year-old woman with a history of advanced hepatocellular carcinoma who developed toxic epidermal necrolysis (TEN) clinically after taking 400 mg sorafenib (Nexavar®, BAY 43-9006) and tosufloxacin orally once per day. Both sorafenib and tosufloxacin were eventually discontinued, and the TEN resolved with corticosteroids and supportive treatment. Clinical physicians should be aware of this possible complication so that early interventions can be made. (Ann Dermatol 23(S3) S404 ~ S407, 2011)

-Keywords-
Hepatocellular carcinoma, Sorafenib, Tosufloxacin, Toxic epidermal necrolysis

INTRODUCTION

Adverse cutaneous reactions to drugs are common occurrences in 2~3% of hospitalized patients1. Severe drug reaction patterns include angioedema, anaphylaxis, exfoliative dermatitis, drug hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). TEN, which is a rare but potentially life-threatening condition, is associated with medications, including sulfonamides, penicillin, and other antibiotics, anticonvulsants, non-steroidal anti-inflammatory drugs, allopurinol, and corticosteroids. Herein, we report a case of a patient diagnosed with sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals-Onyx Pharmaceuticals) and tosufloxacin-induced TEN who was successfully treated with corticosteroids. To our knowledge, TEN associated with sorafenib and tosufloxacin has never been previously discussed in the literature.

CASE REPORT

A 44-year-old woman presented 3 years ago because of chronic hepatitis B-related liver cirrhosis with advanced multifocal hepatocellular carcinoma (HCC). The stage of liver cirrhosis was Child-Pugh’s functional class A. She had received 12 sessions of transcatheter arterial chemoembolization (TACE) repeatedly and one session of radio-frequency ablation since the HCC diagnosis. In combination with TACE, she had also been treated with sorafenib, which is a tyrosine-kinase inhibitor, at the reduced dose of 200 mg orally twice per day since 2008. Two months prior to admission, she underwent percutaneous drainage combined with broad spectrum antibiotics (third generation cephalosporin and cefotaxime) because of an infected intrahepatic biloma secondary to frequent TACE. At that time, the sorafenib therapy was temporarily discontinued. The infected intrahepatic biloma was cured by the above mentioned treatment after 1 month, then administration of sorafenib was restarted at 400 mg once daily, and intrave-
nous antibiotics were switched to oral tosufloxacin (Ozex, SK Chemicals, Seoul, Korea) at 150 mg twice daily.

About 2 weeks after restarting the sorafenib, she was admitted to the emergency department for a generalized erythematous rash and fever. On physical examination, erythematous macules were confluent on >80% of the total body surface with numerous and widespread sheets of flaccid blistering (Fig. 1). Nikolsky’s sign was positive. There were also hemorrhagic crusts on the lips and erosions involving the tongue, oral mucosa, but not the conjunctiva. She evolved rapidly with increased epidermal detachment in the face, neck, thorax, dorsum, and limbs, affecting more than 30% of her body. The patient presented with a temperature of 38.2°C without localized signs of infection. Laboratory studies were normal except for a slightly high C-reactive protein of 3.55 mg/dl (normal, 0–0.5 mg/dl) and an elevated lactate dehydrogenase of 1,017 IU/L (normal range, 95–280 IU/L). Her other medications on admission, included lamivudine, ursodeoxycholic acid, mecobalamin, thiamine, gabapentin, oxycodone, and tosufloxacin, which she had taken for over 2 years without any recent change in dose except for the tosufloxacin. The diagnosis of drug-induced TEN was made based on the clinical history and sorafenib and tosufloxacin administration, which was strongly suspected as the offending medication, and was withdrawn immediately. Tosufloxacin was also discontinued because of the possibility of being the culprit drug. The exposed dermis and eroded mucosal surface were protected with polyurethane foam (Medifoam, DongSung Biopol, Seoul, Korea) and wet gauze. Intravenous hydration and total parenteral nutrition was continued until oral intake was possible without oral pain. She received corticosteroid therapy, given initially as intravenous 5 mg dexamethasone daily and later changed to oral prednisolone. New epithelialization appeared within 15 days, and the lesions gradually resolved (Fig. 2), but hyperpigmentation in the involved areas remained. The patient was discharged with normal oral feeding 8 weeks after admission. She has remained in good health without recurrence of symptoms during 8 months of follow-up.

**DISCUSSION**

TEN, also known as Lyell’s syndrome, is a rare disease of unclear pathophysiology, and its incidence is estimated to be 1.5–2 new cases per million population per year. The disorder seems to be more common among patients with human immunodeficiency virus infection, systemic lupus erythematosus, and malignancy. TEN is a cutaneous
reaction to various precipitating agents, characterized by sudden apoptosis of keratinocytes leading to widespread erythema, mucous membrane erosion, extensive epidermal detachment, and severe constitutional symptoms. Within this spectrum of epidermal necrolysis, detachment of <10% of the total body surface area defines SJS. When >30%, it is defined as TEN, whereas intermediate cases are an overlap of SJS-TEN. Many factors have been proposed as causes of TEN, including adverse reactions to drugs, infections, malignant disorders, and graft-versus-host disease. However, most case reports and studies suggest that TEN is usually an idiosyncratic hypersensitivity to medication. TEN is a serious disease, considering the severity of systemic manifestations, the unpredictable evolution, and the absence of specific therapy.

The diagnosis should be confirmed by skin biopsy showing full thickness necrosis of the epidermis, but, in this case, a skin biopsy was missed unfortunately. Instead, the diagnosis of TEN in our case was based on clinical features which showed skin detachment of >30% of the total body surface area and involvement of mucous membranes. The cause of TEN in our case was considered to be a drug. The most suspected drugs in our patient were sorafenib and tosufloxacin, considering a close temporal correlation between drug exposure and the onset of symptoms. The typical interval between the first drug intake and onset of symptoms is between 1 and 3 weeks. In this case, the characteristic symptoms appeared 2 weeks after restarting sorafenib and tosufloxacin. It remains doubtful why TEN did not occur during the 1.5 years between the initial sorafenib administration and the temporal discontinuation of sorafenib. This was too long to accept as a period of sensitization. Concomitant oral tosufloxacin may have increased the blood level of sorafenib by inhibiting sorafenib metabolism in the liver. Both drugs are metabolized by cytochrome P-450 family enzymes in the liver. Other drugs might be questioned, but the patient had received these drugs for 2 years and these medications were well tolerated and no adverse cutaneous reaction had developed. Sorafenib and tosufloxacin were the only drugs added before the cutaneous lesions appeared.

The pathophysiological mechanisms of TEN remain unknown, but several studies support the hypothesis of an immune mediation. TEN is thought to be initiated by an immune response to an antigenic complex formed by the reaction of drug metabolites with certain host tissues. Genetic susceptibility including HLA genotype might also play a role.

There is no specific treatment for TEN. Discontinuation of the culprit drug is the first step for managing these patients. Additionally, supportive care, including wound care, hydration, and nutritional support forms the basis of treatment. The role of corticosteroids in TEN remains controversial. Although some studies have suggested that systemic corticosteroids are mandatory and life-saving, other studies do not recommend their use, because corticosteroids may increase the risk for infection, delay healing, mask early signs of sepsis, and induce severe gastrointestinal bleeding. We observed the efficacy and safety of corticosteroids administered at an early stage of TEN in our patient.

The SCORTEN, a severity-of-illness score for TEN, is an accurate predictor of mortality in patients with TEN.
Seven predictive factors are included, such as age, malignancy, body surface area detached, tachycardia, serum urea, glucose and bicarbonate. The calculated SCORTEN during the first 24 hours of admission was 3 with a predicted mortality of 35.3%.

Sorafenib, which has gained widespread use in the treatment of advanced HCC, has a good safety profile. The most common cutaneous side effects include skin rash with or without desquamation, alopecia, pruritus, dry skin, and hand-foot skin reactions. Severe skin manifestations such as TEN, as shown in this case, have never been reported. We suspect that tosufloxacin may have contributed to the development of the skin manifestation by altering sorafenib metabolism. Therefore, physicians should be aware of this possible complication, so that early interventions can be made.

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