Toxic Epidermal Necrolysis by Ceftriaxone in Patient with Newly Diagnosed Systemic Lupus Erythematosus

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Toxic epidermal necrolysis (TEN) is a rare disease in absolute numbers with an incidence of 2 cases per million people per year. Most cases of TEN are caused by drugs, but certain infectious diseases may have an impact on the risk. There are rare reports of TEN occurring without history of drug ingestion in systemic lupus erythematosus (SLE), appearing similar to cutaneous lupus and early TEN manifestations, such as erythema multiforme. This report describes a patient with SLE who presented with manifestations of TEN after ceftriaxone treatment. The patient was newly diagnosed with SLE and TEN occurring eight days after cessation of ceftriaxone. Considering possible etiologies, we could not exclude ceftriaxone as the cause of TEN. After intravenous immunoglobulin with glucocorticoid, clinical symptoms improved.

Key Words. Systemic lupus erythematosus, Toxic epidermal necrolysis, Ceftriaxone, Hydroxychloroquine, IV immunoglobulin

Introduction
Toxic epidermal necrolysis (TEN) is an acute, rapidly evolving mucocutaneous reaction, frequently associated with medication use characterized by extensive painful cutaneous and mucosal exfoliation, and systemic involvement that may be life-threatening (1). Common triggers of TEN are antiepileptic drugs such as carbamazepine. Also, allopurinol is the most common cause of Stevens-Johnson syndrome (SJS)/TEN in Europe and Israel (2). However, several drugs except the following drugs can be a cause of TEN (3). One of them is cephalosporin, such as ceftriaxone. Moreover, SLE can present as SJS and TEN, too (4-6). The mortality of TEN approximates 30%. Therefore, differential diagnosis about the cause of TEN is important in SLE patients. We experienced a case presenting TEN in a new diagnosed SLE patient after ceftriaxone administration.

Case Report
A 37 year-old female patient who had facial rash, febrile sense for 2 weeks was admitted to the emergency room. The patient was treated by local dermatologic clinic regarding facial rash using steroid ointment. There was no facial rash improvement; therefore, laboratory tests were checked. She was transferred to our hospital because the test showed elevated liver enzymes. At that time, blood pressure was within normal limit, but the pulse rate 119 bpm and body temperature 38.1°C were increased. In past history, it was non-specific except herbal medication for 4 days before 2 weeks. Nothing unusual was found in familial history. Oral ulcer and mild abdominal tenderness without rebound tenderness were observed. Complete blood count showed decreased white blood cell (WBC) 1,560/mm³ (absolute neutrophil count (ANC) 790), hemoglobin 10.4 g/dL and platelet count 113 K, pancytopenia. It was showed an increased aspartate transaminase/alanine transaminase (AST/ALT) 457/238 (0 ∼ 40) U/L, γ-GTP 44 (0
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~ 38) U/L, and LDH 1,607 (208 ~ 450) IU/L in blood chemistry, but otherwise within normal limit, including urine analysis. The patient was hospitalized in the division of hepatology for evaluation and treatment about hepatitis. Empirical ceftriaxone was started considering infectious fever, and ranitidine, ornithine oxoglurate, and oral prednisolone 10 mg were administered in the light of autoimmune diseases. However, AST/ALT was on the increase continuously. The results of hepatitis viral examination (HAV, HBV, HCV, EBV, and CMV) and autoimmune hepatitis (anti-liver kidney microsomal antibody, anti-smooth muscle antibody, anti-mitochondrial antibody) were all negative. In immunologic test, rheumatoid factor was negative, but anti-nuclear antibody 1 : 640 homogeneous, anti SS-A antibody was positive and anti-dsDNA antibody was over 600 IU/mL. Complements were both decreased: C3 was 20.3 (90 ~ 180 mg/dL) and C4 12.2 (14 ~ 50 mg/dL).

At hospital day 7, ceftriaxone was stopped since fever is not infectious origin. Liver biopsy showed focal macrovesicular steatosis with intralobular degeneration and focal necrosis. Moreover, Masson-Trichrome stain was positive in collagen tissue of the portal tract and reticulin was positive in reticulin framework, too. The result of liver biopsy may be present in SLE. She was diagnosed SLE based on clinical symptoms and laboratory test, and transferred to the division of rheumatology on hospital day 12. At that time of transfer, ANC was decreased to 330/mm³, therefore an increase of prednisolone dosage of up to 50 mg was decided. Three days later, although reduction of AST/ALT was not significant, ANC was elevated to 3,330/mm³. A dose of 400 mg of hydroxychloroquine (HCQ) was prescribed. Confluent erythematous plaques with target lesions developed on the whole abdomen and back with itching sense on the same evening. The rash extended to the extremities, face and neck over 4 days, and then multiple blisters arose on the patient’s abdomen and back (Figure 1). This

![Figure 1. It shows blistered skin lesions in back (A) and upper abdomen (B).](image1)

![Figure 2. It shows skin detachment and new epidermis regeneration. Skin detachment start in back at hospital day 22 (A). Around hospital day 30, almost skin detachment is over and new epidermis go into new regeneration (B).](image2)
Figure 3. It shows skin pathology stained hematoxylin eosin. Epidermis separate from subepidermal layer (A, ×100). Several vacuolization were observed in subepidermal layer (B, ×400). Because total separation from dermal-epidermal junction, it is difficult to observe the vacuolar alteration and solitary necrotic keratinocyte. However, it is not observed that moderate to dense periannexal and perivascular lymphocyte infiltration consistent with SLE.

Discussion

SLE presents various cutaneous manifestations, including blistering condition. The diagnosis of bullous SLE can be difficult since several primary blistering disorders, such as pemphigus vulgaris, bullous pemphigoid, SJS and TEN. Moreover, it is not clear whether patients with SLE have an increased risk for TEN over that of the general population (7). Probably, TEN without causality in SLE should come from keratinocyte apoptosis, common pathology. We considered two possibilities causing TEN in this patient. First, SLE itself can be a cause. Second considerations are drugs, ceftriaxone or HCQ. Aisha et al. have reported a case of TEN and acute generalized exanthematous pustulosis (AGEP) induced by HCQ in a SLE patient (8). Although there is other report about TEN related HCQ (9), times of starting HCQ in both cases differ from our report. Commonly, TEN occurs some days after drug administration. Therefore, one of SLE or ceftriaxone might induce TEN. Unfortunately, there are no definite foci for differential diagnosis, which one is the cause of TEN in SLE or drugs. Pathophysiology of SJS/TEN is still unknown. CD8+ lymphocyte have been identified to play an important role in the process. It seems that ceftriaxone-specific MHC molecule induce specific TCR activation. Cytotoxic T-cells killed autologous lymphocyte and keratinocytes in a drug-specific, perforin/granzyme-mediated pathway restricted to MHC class I. On the other hand, immune-complex and complement infiltration are key factors in skin manifestation of SLE. In our case, there is nothing to observed immune-complex or complement in immunofluorescence. Although we could not find junctional vacuolar alteration or solitary necrotic keratinocyte at lower epidermal level due to epidermal peeling off, HE stain is not suitable SLE-origin TEN because there are no moderate to dense periannexal and perivascular lymphocytic infiltration, with the presence of melanophage (10). According to a report, the onset of TEN-like lupus was insidious, with an initial photodistribution and absence of genital/perianal erosions compared with drug-induced. The mean duration between the onset of the initial rash and epidermal detachment was significantly longer than that of the conventional drug induced TEN (6). In this case, skin lesion occurred acutely with mucosal involvement and distribution of detachment was not limited in photodistribution. Given the acute onset of symptoms, rapid cutaneous progression, prominent mucosal involvement, recent moderate-risk drug exposure, no vasculitic lymphocyte and immunoglobulin infiltration in tissue pathology; therefore, we favored TEN secondary to ceftriaxone.

There is an algorithm for assessment of drug causality in SJS and TEN (ALDEN). It is divided 5 categories by using ALDEN, very unlikely, unlikely, possible, probable, and very probable in
turn. Data from the report showed lower etiologic fraction of cephalosporin related epidermal necrosis, 4.3% (11).

TEN remains a potentially fatal disorder. The typically quoted mortality rate of 20% and 30% was confirmed (12). Established therapies are controversial up to now, and treatments are not different regardless of the etiology. In aspect of the topical treatment, appropriately placed wet dressing may help to avoid adhesion or stricture and infection via skin or mucosa. Also, supportive care in intensive unit is important, such as maintain room temperature, avoiding dehydration and electrolyte imbalance. In addition, various immunomodulating therapies are discussed for SJS/TEN, including IVIG. It is unclear IVIG mechanism to improve SJS/TEN survival. Antibodies in pooled human IVIG block in vitro FAS-mediated keratinocyte necrosis, which is why IVIG is used in the treatment of SJS and TEN (13). Nothing has been decided yet regarding proper dosage of IVIG. The dose has varied from one author to the next (1). There have been arguments against systemic glucocorticoid treatment due to increased mortality related infection (13,14). On the other hand, some reports have shown effects of steroid pulse therapy, preventing ocular complication or not increased mortality (15). We administered prednisolone 1 mg/kg to control SLE activity not TEN. IVIG was prescribed by 50 g/day (1 g/kg/day). We considered ethnic distinctions to decide the dose. Otherwise, there are many immunomodulators to treat TEN, TNF antagonist, thalidomide, cyclophosphamide, cyclosporine A, and etc.

Summary

Our patient recovered rapidly after IVIG treatment. We are following her for 6 months, and she takes HCQ before several months without adverse effects.

References