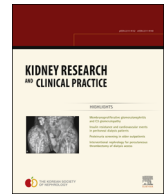




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Case Report

Toxic epidermal necrolysis associated with deflazacort therapy with nephrotic syndrome



Eun Chae Lee, Geun A Kim, Ja Wook Koo*

Department of Pediatrics, Sanggye Paik Hospital, Inje University, College of Medicine, Seoul, Korea

ABSTRACT

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Toxic epidermal necrolysis (TEN) is a drug-related fatal disease. Extensive necrosis of the epidermis can lead to serious complications. This report describes two cases of TEN, associated with deflazacort (DFZ), in two boys, aged 4 years and 14 years, with nephrotic syndrome (NS). The 14-year-old male teenager received DFZ following NS relapse. After 17 days, pruritic papules appeared on the lower extremities. Another case involved a 4-year-old boy receiving DFZ and enalapril. After a 41-day DFZ treatment period, erythematous papules appeared on the palms and soles. Within 3 days, both boys developed widespread skin lesions (> 50%) and were admitted to the intensive care unit for resuscitative and supportive treatment. The patients showed improvement after intravenous immunoglobulin-G therapy. Owing to the rapid, fatal course of TEN, clinicians need to be aware of the adverse effects of this drug when treating cases of NS.

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Introduction

Toxic epidermal necrolysis (TEN) is typically a drug-related fatal disease characterized by necrosis and destruction of the entire epidermal skin layer [1]. Nephrotic syndrome (NS) is treated with steroids such as prednisolone (PD). However, because of the adverse effects, such as osteoporosis, growth retardation, and weight gain, associated with PD treatment, other drugs with fewer side effects, such as deflazacort (DFZ; an oxazoline derivative), have been recommended [2]. Among the 94 patients with NS who received steroid therapy in Sanggye Paik Hospital, Seoul, Korea between 2001 and 2012, three patients who received DFZ developed TEN. We have reported one of these cases previously [3]; herein, we describe the two other cases of TEN related to DFZ in two boys aged 4 years and 14 years.

Case report

Case 1

A 14-year-old boy, who was diagnosed with NS at 8 years of age, received PD as the initial treatment. After 4 months of PD treatment, remission was achieved. However, because of NS relapse, the treatment was switched to DFZ for 14 days; DFZ treatment was then tapered. He was also receiving risperidone (0.5 mg, BID) and atomoxetine (25 mg QD) since 8 years of age for the treatment of mental retardation. After 6 years, he again received DFZ (24 mg TID) daily owing to proteinuria. After a 17-day treatment period, pruritic papules and patches appeared on the lower extremities. He was admitted 19 days after medication was initiated, after the skin lesions indicated an extensive spread within 3 days. Laboratory tests revealed a white blood cell count of 7,040 cells/mm³, C-reactive protein level of 0.3 mg/dL, and negative results for human immunodeficiency virus and *Mycoplasma pneumoniae* antigen. On hospital Day 2, the skin could be easily peeled off, similar to that noted in burn injuries (Fig. 1). Hence, he was transferred to the intensive care unit for infection prevention and conservative care. All medications were

* Corresponding author. Department of Pediatrics, Sanggye Paik Hospital, Inje University, College of Medicine, Dongil-ro 1342, Nowon-gu, Seoul, Korea.

E-mail address: koojw9@paik.ac.kr (JW Koo).



Figure 1. Typical pattern of toxic epidermal necrolysis: erythema, blistering, and full-thickness epidermal loss is seen over the entire body.

discontinued immediately. Intravenous immunoglobulin-G (IV-IG; total, 4.51 g/kg) was administered according to the severity of the skin lesions. After 18 days of treatment, the skin lesions improved. The patient needed conservative management, and was discharged on hospital Day 25. After discharge, the NS has been controlled by switching the treatment to PD, and the patient has consistently taken risperidone. Thus far, he has not experienced any skin complications.

Case 2

A 4-year-old boy who was diagnosed with NS was receiving DFZ (24 mg TID) and enalapril (5 mg QD). After 41 days, he presented with papules and blisters around the mouth and on the palms and soles (Fig. 2). He was suspected to have TEN and was hospitalized.

His vital signs were stable, although he had a fever. The initial white blood cell count was 14,720 cells/mm³ and the C-reactive protein level was 1.4 mg/dL. The other laboratory findings were normal.

Erythematous papules and blisters rapidly spread on his body ($\geq 50\%$) within 3 days. The administration of oral steroids was discontinued. Ceftriaxone was injected, and IV-IG (total, 4 g/kg) was administered for 13 days according to the extent of skin complications. From Day 20 after hospital admission, the patient showed improvement in the symptoms, and was subsequently discharged. Thereafter, the medication was switched to PD, and he has not experienced a relapse thus far.

Discussion

TEN is a rare but life-threatening disease that involves the skin and mucosa, and is usually caused by certain drugs [1].



Figure 2. Erosions and crusts on the lips and multiple bullae on the face and chest.

The extent of epidermal involvement in TEN is more than 30% [1,4].

A few recently published cases indicate that TEN might be induced by steroid use [3,5,6]. In particular, at our center, 40 patients treated with PD did not develop TEN, but three of 54 patients treated with DFZ developed TEN. In Case 1, despite the initial treatment with PD and DFZ, no skin complications developed at that time. However, after readministration of high-dose DFZ for more than 2 weeks, TEN developed. After remission was achieved, rashes did not reappear even after switching the treatment to oral PD. PD has also been reported to potentially cause Stevens–Johnson syndrome (SJS) [7]. TEN is considered a delayed-type hypersensitivity reaction [1]. The reaction severity decreases following the discontinuation of drug administration and develops more rapidly on drug readministration.

In Case 1, risperidone and atomoxetine were administered simultaneously. It is unclear whether drug interactions were involved in the development of TEN. However, these drugs were administered 6 years previously and the patient did not present side effects at that time. Consistent with the findings in Case 2, Kim et al [3] reported that TEN developed in a patient with NS treated with DFZ and enalapril. After approximately 4 weeks of treatment, the condition progressed from erythematous papules to TEN. Captopril was reported to possibly cause TEN [8], whereas enalapril may be a causative agent for TEN when combined with DFZ [3]. Enalapril and captopril have been suggested to be powerful acantholytic drugs *in vitro*, and the active amide group of both drugs could induce acantholysis [9]. However, Papay et al [10], in their extensive review of SJS/TEN, have classified both drugs as “drugs commonly used but probably not associated with SJS/TEN.” Kim [5] and Kim et al [6] also reported cases of SJS and TEN caused by the use of DFZ (Table 1). Their patients did not receive any other medication, except for DFZ, over 8 weeks. TEN is considered to be associated with exposure to an agent during an 8-week period prior to disease onset [1]. To confirm the relationship between TEN and DFZ, a rechallenge would be helpful. Kim [5] has suggested that DFZ may be a possible cause of SJS, based on the results of skin tests and provocation tests using DFZ. In the present cases, a rechallenge with DFZ could not be performed due to ethical reasons. The relationship between corticosteroids, especially DFZ, and TEN remains controversial, and its exact mechanism is not known [11]. Roujeau et al [11] suggested that the risks were particularly

Table 1. Demographics and clinical characteristics of recovered patients

Patient no.	Age (y)	Sex	Underlying disease	Causative agent	Duration of DFZ Tx.	Combined agent	Diagnosis	Treatment	Refs
1	14	M	NS, MR	DFZ	17 d	Risperidone, atomoxetine	TEN	IV-IG	Case 1
2	4	M	NS	DFZ	41 d	Enalapril	TEN	IV-IG	Case 2
3	14	M	MN stage 3	DFZ	4 wk	Enalapril	TEN	Methylprednisolone, IV-IG	[3]
4	11	M	NS	DFZ	8 wk	None	TEN	IV-IG	[6]

DFZ, deflazacort; IV-IG, intravenous immunoglobulin G; MN, membranous nephropathy; MR, mental retardation; NS, nephrotic syndrome; PD, prednisolone; TEN, toxic epidermal necrolysis.

increased for patients who had recently started receiving therapy (within 2 months) with most of the commonly questionable agents, including corticosteroids. An immunosuppressive mechanism involving corticosteroids might play a role in the pathophysiology of SJS/TEN [12]. In numerous cases of SJS/TEN, the use of multiple medications or co-use of drugs may cause the development of SJS/TEN [10]. However, most importantly, the only medication that was common between the cases and was taken within 8 weeks prior to disease onset was DFZ. Therefore, we hypothesized that DFZ was more likely to be the potential cause of TEN, compared with other medications, although we could not exclude the possible additional role of enalapril in Case 2.

In most cases, TEN is almost exclusively attributed to drugs; however, infections by viruses, bacteria, and mycobacteria could trigger the development of TEN in association with drugs [1]. Because infection tests, such as herpes simplex virus tests, other than those for *M. pneumonia* and human immunodeficiency virus, were not performed in the present cases, we could not clearly exclude the possibility of an infectious origin. Nevertheless, from the viewpoint of immune suppression, it should be noted that TEN did not develop in patients treated with PD.

Several cases have demonstrated an association between secondary glomerular nephritis such as that in systemic lupus erythematosus and TEN [13]. In the present cases, renal biopsies were not performed owing to the parents' refusal to undergo this examination; however, no serological abnormalities were noted with regard to the rheumatoid factor, anti-nuclear antibody, and complement levels.

The pathophysiology of TEN remains controversial [1]. When cytotoxic T lymphocytes come in contact with target cells, the Fas–Fas ligand pathway is induced and triggers apoptosis in TEN [14]. Treatment using IV-IG may be a pathogenetic approach. IV-IG includes autoantibodies against normal proteins such as Fas. IV-IG likely affects a combination of many pathways that results in blocking of the interaction of Fas with FasL [14]. In patients with TEN, an IV-IG dose of 2–4 g/kg has been recommended for treatment [1,15]. In the present cases, the patients were administered a total dose of 4.51 g/kg over 18 days and 4 g/kg over 13 days. The IV-IG was injected at a dose of 2 g/kg during the first 5 days of the onset of skin eruption, which was reduced depending on the severity of the skin lesions. The IgG levels were within the normal range. No adverse effects related to IV-IG therapy, including cephalgia, low-grade fever, flushing, chills, and myalgia, were noted [15]. The patients needed to be isolated and to be administered supportive care such as wound management, fluid replacement, respiratory and nutritional support, careful monitoring,

and pain management. When TEN develops, patients require extensive and prolonged treatment and hospitalization.

The reason for the development of TEN in DFZ patients and not in PD patients is not yet clear. Moreover, the effect of the combination of medications or infection on the development of TEN is unclear. Nevertheless, because of the rapid, progressive, and fatal course of TEN associated with DFZ, we believe that it is essential to perform additional multilateral research and safety evaluations of DFZ, and that clinicians should be aware of the serious side effects of this drug when treating cases of NS.

Conflict of interest

The authors declare that they have no conflict of interest.

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