

## Case report

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# 소아 신증후군 환자에서 데플라자코트 치료 중 발생한 다형 홍반 3례

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## Three Cases of Erythema Multiforme Developed during Deflazacort Therapy in Children with Nephrotic Syndrome

Erythema multiforme (EM) is an acute mucocutaneous disorder involving the skin, mouth, eyes, and genital organs. It is classified into EM minor and EM major according to the involvement of the mucosal membrane. Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN) belong to EM major. Compared to EM minor, SJS presents with more severe and progressive symptoms, and has a higher mortality rate. Corticosteroids are used in the treatment of EM. We report three cases of EM (two cases of EM minor and one case of SJS) that developed during treatment with oral corticosteroid (deflazacort; Calcort<sup>®</sup>) in children with nephrotic syndrome.

**Key words:** Erythema multiforme, Stevens-Johnson syndrome, Nephrotic syndrome, Deflazacort

### Introduction

Erythema multiforme (EM) is a cell-mediated immune reaction characterized by skin exanthema [1]. EM is classified as EM minor and EM major according to the involvement of the mucosal membrane [1]. EM minor is characterized by target-like skin lesions. EM major has been characterized by a mucosal involvement of the respiratory tract, gastrointestinal tract and anogenital tract, and is also termed Stevens-Johnson syndrome (SJS) or toxic epidermal necrosis (TEN) according to the extent of mucosal involvement [2, 3]. Although the pathophysiology of EM has not been elucidated, drugs and infections have been reported as major causes [4]. In the treatment of EM, only supportive management and

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immunomodulating treatments, such as corticosteroids and intravenous immunoglobulin (IVIg), are important to relieve the patient's skin condition and to decrease ocular complications [4-6]. In our experience, patients with nephrotic syndrome received deflazacort (Calcort<sup>®</sup>), an oxazoline derivative of prednisolone. Herein we report three cases of EM (one case of SJS, two cases of EM minor) during treatment with deflazacort.

## Case reports

### Case 1

On July 2011, an 11-year-old boy was admitted with pruritic erythematous that involved dark red macules with bullae formation covering the entire body. Starting 6 days before admission, the maculopapular rash had developed from his palm and expanded to face and trunk, with the skin lesions accompanied by lip swelling. About that time, he had been prescribed and began to use medications (including oximac-type nonsteroidal anti-inflammatory drugs, NSAIDs) from a local medical center for cough and sputum. About 4 weeks before the present hospitalization, he had been in hospital due to facial edema and scrotal swelling. Laboratory findings were as follows: serum protein/albumin 4.0/1.8 g/dL, blood urea nitrogen (BUN)/serum creatinine 12/0.3 mg/dL, spot urine protein/creatinine ratio 2.0, 24hr urine protein 1.1 g/m<sup>2</sup>. He had then been diagnosed with the first episode of nephrotic syndrome and had taken deflazacort (60 mg/m<sup>2</sup>/day for 6 weeks). He had no history of known drug allergy and recent vaccination. On physical examination, he appeared acutely ill with multiple vesiculopapular rashes and pruritic bullae with face, trunk and anorectal junction involvement. Mucosal erosion of the lips and oral cavity, and conjunctival injection and eye discharge were evident. Vital signs were: blood pressure 123/77 mmHg, heart rate 98 beats/minute, respiratory rate 18/minute, and body temperature 36.6°C. His weight was 27.6 kg (50 percentile) and his height 137 cm (25 percentile). Laboratory findings were: hemoglobin 15.1 g/dL, white blood cell

count 7,100/ $\mu$ L, platelet count 255,000/mm<sup>3</sup>, C-reactive protein level 0.7 mg/dL, erythrocyte sedimentation rate 13 mm/hour, total protein 6.4 g/dL, albumin 3.7 g/dL, BUN/serum creatinine 7/0.6 mg/dL, aspartate transaminase/alanine transaminase 26/20 IU/L, sodium 135 mEq/L, and potassium 3.6 mmol/L. *Mycoplasma pneumoniae* and herpes simplex virus IgG and IgM were negative. Antibodies to Coxsackie virus B type 2 and 5 were detected using ELISA. There was no laboratory evidence of autoimmune disease. Urinalysis indicated normal values.

On the second day of hospitalization, new skin lesions developed with pruritic macule and bullae on the face (Fig. 1). The multiple bullae changed to a dark red color with pruritus and spread over the entire body. Also, erosive mucosal lesions persisted in the oral cavity, lips, and anorectal junction. The diagnosis was SJS (Fig. 2). No corneal lesion was evident on an ophthalmological exam. We applied bullae aspiration and topical steroid ointment and maintained deflazacort (60 mg/m<sup>2</sup>/day). On the fifth day of admission, pain and skin lesions were



**Fig. 1.** Photograph showing multiple bullae on face and lips in a boy with Stevens-Johnson syndrome (Case 1).



**Fig. 2.** Photograph showing ruptured bullae on anorectal mucosa in a boy with Stevens-Johnson syndrome (Case 1).

improved with desquamation of hands, feet, face, and trunk. After 17 days of admission he was discharged with skin lesions completely resolved. Oral corticosteroid was maintained according to the treatment protocol of the initial episode of a nephrotic syndrome.

### Case 2

On November 2011, a 5-year-old female patient was admitted with target-like skin rash lesions on palms, soles of the feet, and trunk, with pain and itchy sensation. About 5 weeks before this hospitalization, she had been admitted to our hospital because of generalized edema. Laboratory findings were as follows: serum protein/albumin 4.5/1.3 g/dL, BUN/serum creatinine 10/0.1 mg/dL, spot urine protein/creatinine ratio 9.7, 24hr urine protein 1.96 g/m<sup>2</sup>. She had been diagnosed with the first episode of nephrotic syndrome and had begun to take deflazacort (60 mg/m<sup>2</sup>/day for 6 weeks). She had no known history of drug allergy and recent vaccination.

On physical examination, she presented with slightly painful and pruritic erythematous patches with target-shaped and millet to pea-sized lesions on the soles, palms, and trunk. There was no mucosal involvement. On the day of admission, she was diagnosed with EM and continued to receive the same dose of deflazacort, with the addition of topical steroid ointment.

### Case 3

On October 2013, a 2-year-old male patient was admitted with papular rashes with itchy sensation on the perioral area, palms, soles, perianal area and trunk. About 5 weeks before this hospitalization, he was diagnosed with the first episode of nephrotic syndrome and had been prescribed deflazacort (60 mg/m<sup>2</sup>/day for 6 weeks). At that time, laboratory findings were as follows: serum protein/albumin 3.6/1.5 g/dL, BUN/serum creatinine 13/0.5 mg/dL, spot urine protein/creatinine ratio 18.2, 24hr-urine protein 4.65 g/m<sup>2</sup>. He had no history of known drug allergy and recent vaccination. On physical examination, he presented with purulent and vesiculopapular rashes accompanying a pruritus that covered his palms and soles to the trunk, without mucosal involvement. He was diagnosed with an exudative EM. A topical antibacterial agent was applied to control a secondary bacterial infection and the oral corticosteroid was continued without dose reduction. On the fourth day of hospitalization, erythematous papular rashes were improved and there was no recurrence of skin lesion. He was discharged on day 9 of hospitalization.

### Discussion

EM is an immune-mediated condition presenting with skin eruption that is classified into major and minor according to the involvement of mucosal membrane [1]. EM minor is a mild cutaneous lesion established by Ferdinand von Hebra in 1866 [1]. If mucosal membrane is involved, it is limited to the oral cavity only. EM major is characterized by mucosal membrane erosion, widespread blisters, and skin detachment; it is also termed SJS (named by Albert Mason Stevens and Frank Chambliss Johnson in 1922 and published in Journal of the American Academy of Dermatology) and TEN [1]. SJS and TEN has <10% and >30% mucocutaneous involvement of the total body surface area, respectively [2]. EM most frequently occurs between 20 and 40 years of age, with males having higher morbidity [2]. The mortality of EM major is approximately 25% because SJS/

TEN can induce hypovolemia by the loss of water and because of secondary infection, and may lead to shock with multi-organ failure followed by death [4]. SJS also displays dermatologic complications with scarring and xeroderma, and ophthalmic complications with ophthalmoxerosis and photophobia [4].

Although the pathogenesis of EM remains debatable, several studies reported allergic reactions by immune complex-mediated delayed hypersensitivity after exposure to viral infection, drugs, or chemical products [3]. The major causes of SJS are common drugs, such as antibiotics (penicillin and sulfonamide), anti-epileptic drugs (phenytoin, carbamazepine, barbiturate, and allopurinol) and oxicam-type NSAIDs [5]. SJS can also arise from infections, such as herpes simplex, mycoplasma, human immunodeficiency virus (HIV), enterovirus, Epstein-Barr virus (EBV), influenza virus, hepatitis, and mumps [3-5].

Drug-induced EM occurs due to the apoptosis of epithelial cells and a cascade of inflammatory reactions mediated by being concerned tumor necrosis factor-alpha and interferon-gamma [6]. Treatment of acute EM involves down regulation of the immune reaction. Presently, the three patients received deflazacort as treatment of their initial episode of nephrotic syndrome. Deflazacort is a derivative of prednisolone that was introduced in 1969 to reduce the side-effects of prednisolone [7]. Although deflazacort was recalled in 1998 due to insufficient evidence of differences in its side effects, recent studies have supported its use as the long-term initial treatment in patients who have a higher probability of metabolic side effects [8]. EM has been rarely reported as the side effects for deflazacort.

Blanca et al, reported on the comparison of outcomes between immune therapy (IVIg, steroid therapy) and conservative treatment (dressing and supportive care) in the acute phase of SJS/TEN [9]. Patients treated with IVIg and steroids displayed less time to full recovery, shortened term of admission, and less ocular and long-term complications than those treated conservatively [9]. Although steroids are used therapeutically for EM, the present three cases (one case SJS, two cases EM minor) highlight the development of EM during steroid therapy

in children with nephrotic syndrome. Jo et al, reported the development of EM in a patient receiving oral prednisolone during nephrotic syndrome and described the improvement by the injection of intravenous methylprednisolone without complications [10]. In our case of SJS, the patient's symptoms developed after taking the medicines including analgesics for an upper respiratory infection 3 days before. Also, Coxsackie virus IgM was positive. Therefore, the most possible causes in this case seem to be drugs and infection. When we compared the SJS case with the EM minor cases, the latter two had no evidence of infection and drug history, except for deflazacort.

Considering that all three patients had been taking deflazacort (60 mg/m<sup>2</sup>/day) for several weeks, bone marrow suppression due to the steroid therapy may have led to their vulnerability to viral infection. Also, the immune-compromised state owing to a nephrotic syndrome could be predisposing factor of EM. Therefore, these risk factors should be kept in mind in the treatment of nephrotic syndrome. Also, EM may occur as a delayed hypersensitivity to chemical products derived from deflazacort. Although our cases occurred under the treatment of a nephrotic syndrome with deflazacort, the time to achieve remission could be shortened without complication by maintaining deflazacort without reducing the dose.

In conclusion, EM may develop during corticosteroid treatment in children with nephrotic syndrome. However, we suggest that treatment with corticosteroids should be maintained to reduce the severity of disease and morbidity of complications.

## 한글요약

다형 홍반은 피부, 구강, 입술 및 생식기 등을 침범하는 급성 피부점막 질환으로 점막 침범 여부에 따라 다형 홍반 minor와 다형 홍반 major로 분류된다. 스티븐스-존슨 증후군과 독성표피괴사용해는 다형 홍반 major에 속하는데, 이들은 증상이 심하고 진행성이며 높은 사망률을 보인다. 코르티코스테로이드는 현재 다형 홍반의 치료제로 사용되고 있다. 저자들은 신증후군을 가진 소아 환자에서 경구

코르티코스테로이드인 데플라자코트를 사용하던 중 발생된 3개의 다형 홍반 증례를 보고하는 바이다.

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