□ Case Report □

Steroid and enalapril therapy - possible cause of toxic epidermal necrolysis

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Toxic epidermal necrolysis (TEN) is a rare, acute and life-threatening cutaneous drug reaction. TEN is characterized by the sudden onset of extensive necrosis in the epidermis and frequent mucous membrane involvement. The pathogenesis has not yet been elucidated. In addition, no particular treatment for TEN has been established. We report a case of TEN in a 14-year-old-boy, which might have been caused by steroids with enalapril treatment for membranous nephropathy. He recovered after intravenous immunoglobulin therapy. **(Korean J Pediatr 2006;49:332-336)**

Key Words : Steroid, Enalapril, Toxic epidermal necrolysis, Intravenous immunoglobulin

Introduction

Toxic epidermal necrolysis (TEN) is a very rare mucocutaneous disease characterized by necrosis and extensive destruction of the epidermis, showing a high death rate despite proper treatment[1]. It is related particularly to sulfonamides, anticonvulsants (phenytoin, phenobarbital), penicillin antibiotics and non-steroidal anti-inflammatory agents and is rarely caused by steroid[2]. The presence of a sulfa moiety within the drug structure has been postulated to be a major contributing factor to the likelihood of the development of cutaneous reactions[2]. The mechanism by which this occurs is not fully understood.

Recently a fas receptor was found to play an important role in the cell apoptosis of keratinocytes in toxic epidermal necrolysis. Intravenous immunoglobulin is increasingly used in treating this disease and, as a result, the rise of the survival rate and the shortening of the treatment period are reported[3]. Although the infusion of immunoglobulin has not been established as a treatment method for toxic epidermal necrolysis throughout the world, there have been a number of reports on treatment with infusion of immunoglobulin[4, 5].

We report, together with a literature review, a case of toxic epidermal necrolysis, which might have been caused by steroid with enalapril treatment in a patient with membranous nephropathy treated with high dose intravenous immunoglobulin.

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Case Report

A 14-year-old boy visited Sanggye Paik Hospital in April 2004 with a chief complaint of generalized edema. 24-hour urine collection showed nephrotic-range proteinuria, and his disease was diagnosed as nephrotic syndrome (membranous nephropathy, stage III) by renal biopsy. Since two weeks before being admitted to the hospital, the patient had been taking only oral angiotensin-converting enzyme inhibitors (enalapril, 5 mg) everyday with steroid (deflazacort, 72 mg) every other day. However, he was readmitted for erythematous papules that started 3 days ago. Erythematous papules spread to the forehead, the face, the neck and the body, and developed into erosion of the oral mucosa accompanied with cough and low-grade fever.

When the patient was admitted, his blood pressure was 130/80 mmHg, pulse rate 92 beats/min, respiratory rate 20 times/min, and body temperature 38.2℃. Corneal ulcer or conjunctival inflammation was not found but erosion of oral mucosa was observed. The rest of his physical findings were normal. There was neither cardiac murmur nor other unusual physical findings. There were extensive dark-red erythematous papules over the face and the erosion of oral mucosa, and dark-red erythematous papules

fused with one another scattered around the whole body surface. In the complete blood count test, the level of white blood cell count was normal at 6,630/mm^3, and findings from liver function tests and renal function tests were all normal. Serum protein was 5.60 g/dL and albumin 3.39 g/dL, which were slightly below the normal levels. In the 24-hour urine collection, proteinuria of around 2,580 mg/24hr was observed but red blood cells were not detected in the urine. The erythrocyte sedimentation rate (ESR) was 24 mm/hr and C-reactive protein (CRP) was 0.4 mg/dL. Blood culture tests performed on admission were negative. Mycoplasma antibody titer was measured at around 1 : 40, and the result of the test for varicella zoster virus was negative. In the Tzank test on the vesicles, no polynucleated cells were found. The result of the bacterial culture test on the blisters in the skin was negative. In the renal function test and urinalysis afterwards, the worsening of nephrotic syndrome was not observed. Chest X-ray was generally normal.

Skin biopsy was done on the 3rd day of admission. Subepidermal blisters and necrosis of epidermal keratocytes were found. Mild perivascular lymphocytic infiltration was also found. It was compatible with toxic epidermal necrolysis (Fig. 1).

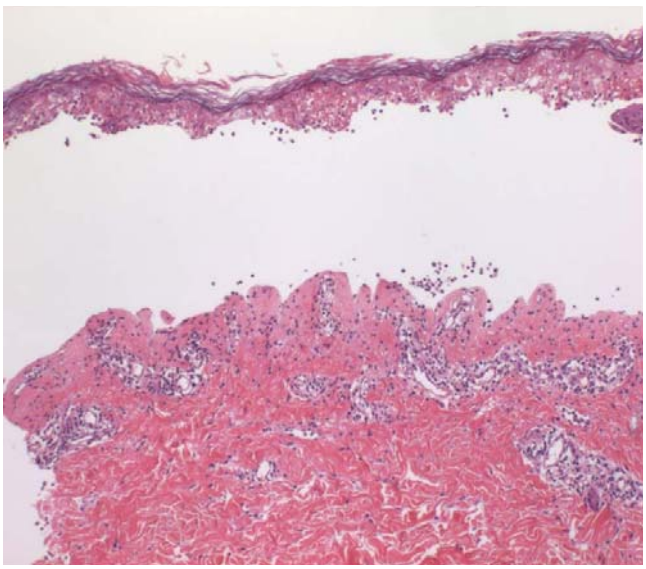

Fig. 1. Skin biopsy was compatible with toxic epidermal necrolysis. a) Subepidermal blister. b) Necrosis of epidermal keratocytes. c) Mild perivascular lymphocytic infiltration. H&E stain, ×40.

Treatment and progress (Fig. 2) : From the 2nd day of admission, the erythematous papulomacular rash spread throughout the whole body, and a target sign was observed at the center of the lesion. From the 3rd day of admission, a 1-2 mm large blister formed in the center of the dark-red erythematous patches and erythematous patches and small blisters fused with each other, forming large blisters and showing Nikolsky sign. We began pulse infusion of corticosteroids (methlyprednisolone). On the 4th day of admission, large blisters formed throughout the whole body, and separation between epidermis and dermis occurred at around 40% of the whole body surface area, starting from the face and the trunk. Since then, the formation of large blisters and separation between dermis and epidermis continued further, and the separated epidermis necrotized. On the 5th day of admission, the patient complained of bilateral ocular pain. No corneal damage was observed but conjunctival inflammation was found.

From the 6th to 8th day of admission, despite several infusions of methlyprednisolone, the skin lesions did not improve and were even more aggravated (Fig. 3). On the 9th day, immunoglobulin was administered at a rate of 0.25

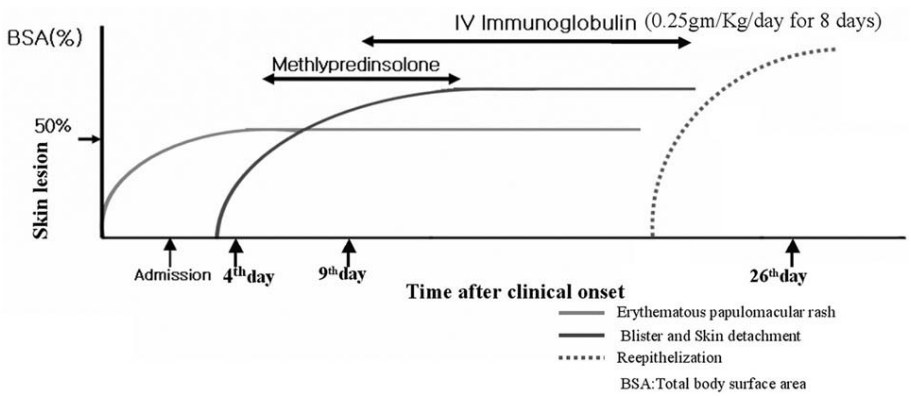

Fig. 2. Skin lesion and treatment after clinical symptom onset.

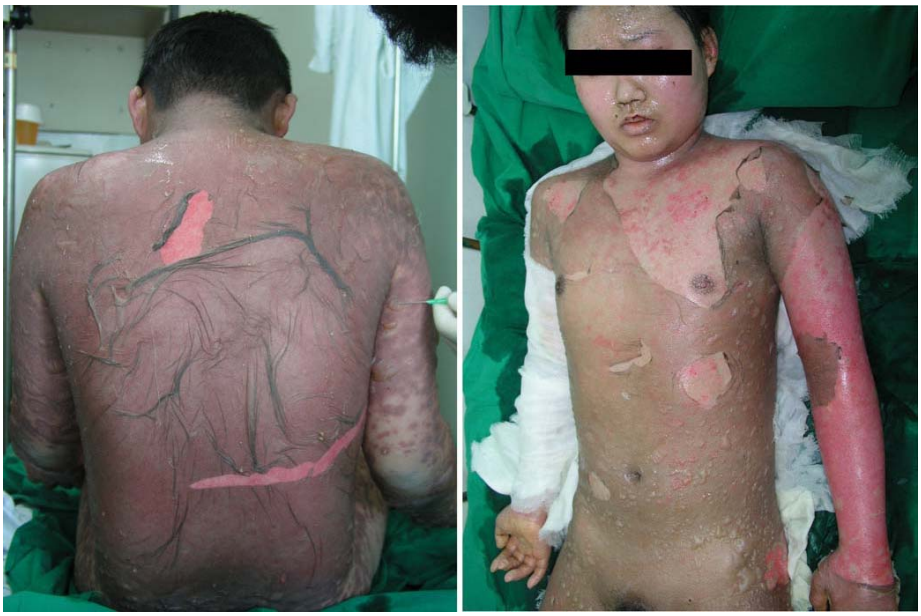

Fig. 3. Extensive epidermal detachment more than 60 percent of total body surface.

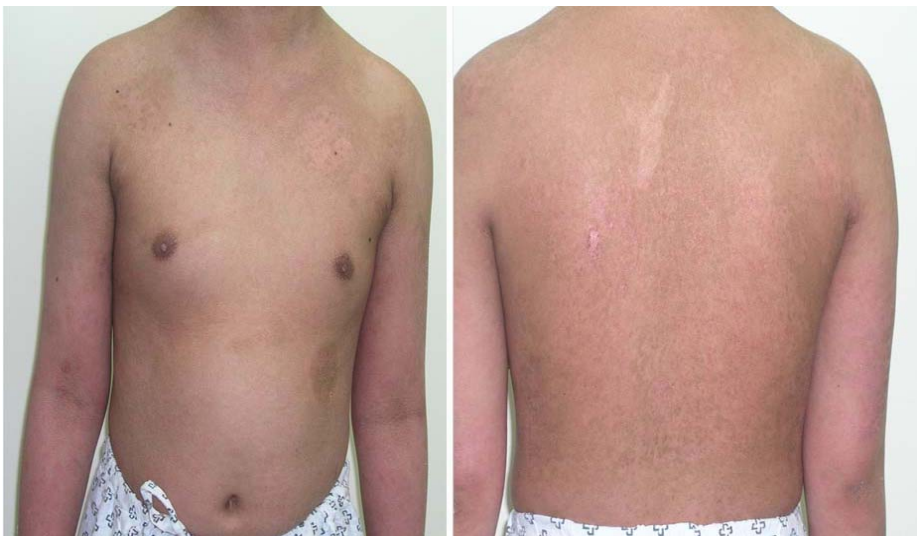

Fig. 4. After intravenous immunoglobulin infusion, reepithelization was completed on the face and trunk, and extremety.

g/kg/day for 8 days. On the 12th day of admission, the scaling of the epidermis was observed over 65% of the whole body surface area but, since the infusion of immunoglobulin, re-epithelization was observed over some parts of the skin. On the 20th-26th day of admission, re-epithelization occurred over most parts of the body (Fig. 4), and the patient was discharged without side effects of immunoglobulin. He remains well and has not experienced any recurrence of skin lesions and is currently taking oral prednisolone.

Discussion

Hypersensitivity reaction to drugs is considered to be the main cause of TEN[2, 6]. Representative drugs include sulfonamide, anticonvulsants (phenytoin, phenobarbital), penicillin antibiotics and nonsteroidal anti-inflammatory agents, but incidences of cases caused by steroid are rarely reported[6]. There is no particular treatment established for TEN. There have been reports on the effects of cortico-

steroid[7], plasmapheresis[8], and cyclosporine[9], but these methods are controversial because they may increase the possibility of infection as they suppress immunity and most patients begin to recover only after 3-5 days regardless of treatment.

Recently Viard et al.[3] and Paul et al.[10] reported that a large number of fas receptors (fas ligand or CD95 ligand) are manifested in keratinocytes in patients with TEN and the apoptosis of cells resulting from the binding of fas with fas receptors is the main cause of the disease. In addition, they reported that anti-fas immunoglobulin contained in intravenous immunoglobulin blocks fas receptors and prevents fas-receptor-mediated keratinocyte apotosis. With regard to their experiment in which they administered 10 TEN patients with intravenous immunoglobulin at a dose of 0.2-0.75 g/kg/day for four days, they reported that the development of lesions stopped within 24-48 hours and re-epithelization was completed within 2 weeks of administration.

Also there are reports that the administration of corticosteroid does not stop TEN but delays the occurrence and treatment of lesions and that it may cause TEN[11].

It is difficult to identify drugs that induce TEN based on the patients' medication history because there is no particular test method, but the drug administered 7-21 days before the appearance of lesions is generally assumed to be the cause[11]. In the present case, the patient taken oral corticosteroids and enalapril for two weeks before the occurrence of lesions, so oral corticosteroid and enalapril are considered to have caused TEN. Roujeau et al.[2] reported that corticosteroids significantly increased the risk of TEN, although the pathogenesis is unclear. So far it was not reported that enalapril induced TEN and appears to have a few side effects, particularly skin rash compared to other ACE inhibitors[12]. However, captopril, another ACEI, was reported as a possible cause of TEN[13] and enalapril which also contains a sulfa moiety within its structure may be a causative agent for TEN. We used oral steroid (deflazacort) and enalapril combination therapy in this patient. Since the pathogenesis is not fully understood the main cause for TEN can not be determined. Unfortunately a re-challenge test with both agents could not be performed due to the parents' refusal.

The reason for skin lesions not reappearing after oral deflazacort was changed to oral prednisolone after TEN remission, is not yet clear. It is also not clear what effect of enalapril might have had on the development of TEN.

High-dose intravenous immunoglobulin may cause acute renal failure[14], but blood urea nitrogen, serum creatinine and urinalysis were normal after it had been administered. Besides side effects in the kidneys, hypotension, hypertension, headache, fatigue, hot flash, etc. may result from the use of intravenous immunoglobulin but these side-effects disappear spontaneously if the infusion rate goes down or infusion is stopped temporarily.

Treatment using intravenous immunoglobulin may be a pathogenetic approach, advantageous in that it does not increase the risk of infection, so it may be one therapy to be applied in treating TEN.

We experienced a case of toxic TEN caused by the use of steroid with enalapril in a child suffering from nephrotic syndrome, which we treated with intravenous immunoglobulin.

한 글 요 약

부신 피질 호르몬제와 안지오텐신 수용체 길항제 사용 후 발생한 독성 표피괴사 증후군

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독성 표피괴사 증후군(Toxic epidermal necrosis)은 매우 드문 수포성 피부 질환으로 표피 전층의 괴사와 박리를 특징으로 하는 질환이며, 적절한 치료에도 불구하고 높은 사망률을 보이는 질환이다. 대부분의 독성 표피괴사 증후군의 약물과 연관이 있으며, 대표적인 약물로는 설폰아마이드(Sulfonamide), 항경련제(Phenytoin, Phenobarbital), 페니실린계 항생제, 비스테로이드성 소염제 등이며, 드물게 부신 피질 호르몬제에 의한 발병도 보고되고 있다. 최근 독성 표피괴사 증후군에서 각질 세포의 세포고사(cell apoptosis)에 Fas 수용체가 중요한 역할을 한다고 알려진 후 치료에 면역 글로불린 사용이 점차 늘어나고 있으며, 생존율의 증가와 치료기간의 단축이 보고되고 있다. 국내에서는 아직 독성 표피괴사 증후군에서 면역 글로불린정주가 치료방법으로 확립되지 않았지만 몇몇의 경우에서 면역 글로불린 정주로 치료한 경험들이 보고되고 있다. 저자들은 막성 신염 환아에서 부신 피질 호르몬제와 안지오텐신 수용체 길항제 사용 후 발생한 독성 표피괴사 증후군에서 면역 글로불린을 사용하여 치료한 1례를 경험하였기에 문헌 고찰과 함께 보고하자 한다.

References

1) Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau

JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Arch Dermatol 2000;136:232-7.
2) Roujeau JC, Stern RS. Severe cutaneous adverse reactions to drugs. N Engl J Med 1994;331:1272-85.
3) Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science 1998;282:490-3.
4) Tristani-Firouzi P, Petersen MJ, Saffle JR, Morris SE, Zone JJ. Treatment of toxic epidermal necrolysis with intravenous immunoglobulin in children. J Am Acad Dermatol 2002;47:548-52.
5) Prins C, Kerdel FA, Padilla RS, Hunziker T, Chimenti S, Viard I, et al. Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins : multicenter retrospective analysis of 48 consecutive cases. Arch Dermatol 2003;139:26-32.
6) Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS, Jick H, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis : a population-based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol 1990; 126:43-7.
7) Lyell A. Toxic epidermal necrolysis (the scalded skin syndrome) : a reappraisal. Br J Dermatol 1979;100:69-86.
8) Kamanabroo D, Landgraf SW, Czarnetzki BM. Plasmapheresis in severe drug induced toxic epidermal necrolysis. Arch Dermatol 1985;121:1548-9.
9) Hewitt J, Ormerod AD. Toxic epidermal necrolysis treated with cyclosporin. Clin Exp Dermatol 1992;17:264-5.
10) Paul C, Wolkenstein P, Adle H, Wechsler J, Garchon HJ, Revuz J, et al. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. Br J Dermatol 1996; 134:710-4.
11) Revuz JE, Roujeau JC. Advances in toxic epidermal necrolysis. Seminars Cut Med Surg 1996;15:258-66.
12) McFate SW, Davies RO, Gabriel MA, Kramsch DM, Moncloa F, Rush JE, et al. Tolerance and safety of enalapril. Br J Clin Pharmacol 1984;18 Suppl 2:249-55.
13) Alkurtass DA, Al-Jazairi AS. Possible Captopril-Induced Toxic Epidermal Necrolysis. Ann Pharmacother 2003;37: 380-3.
14) Phillips AO. Renal failure and intravenous immunoglobulin. Clin Nephrol 1992;36:83-6.