

A case of steroid-induced psychosis in a child having nephrotic syndrome with toxic epidermal necrolysis

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= Abstract =

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are rare, life-threatening mucocutaneous diseases, usually attributable to drugs and infections. Corticosteroids have been used in the management of TEN for the last 30 years. This remains controversial and is still much debated. TEN can occur despite administration of high doses of systemic corticosteroids. The psychiatric side effects of corticosteroids can include headache, insomnia, depression, and mood disorders with or without psychotic episodes. Steroid-induced psychosis is dealt with by tapering or discontinuing the steroid; antipsychotics are also sometimes used. We report a case of an 11-year-old boy who was admitted with TEN. He had also been diagnosed as having nephrotic syndrome in the past. Remission was achieved through induction therapy and by maintaining the use of steroids. After a full-dose intravenous dexamethasone for TEN, he showed psychotic symptoms. We diagnosed him as having steroid-induced psychosis. We tapered the steroid use and initiated an atypical antipsychotic medication, olzapine and intravenous immunoglobulin (IV-IG). His symptoms dramatically improved and he was discharged. (*Korean J Pediatr* 2010;53:437-441)

Key Words: Nephrotic syndrome, Toxic epidermal necrolysis, Steroid-induced psychosis

Introduction

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are rare, life-threatening mucocutaneous diseases, usually attributable to drugs and infections¹. Corticosteroids have been used in the management of TEN for the last 30 years. Their use has been much debated and remains controversial². TEN can occur in spite of high dose of systemic corticosteroids³. The psychiatric side effects of corticosteroids can include headache, insomnia, depression, and mood disorders (including bipolar and manic states) with or without psychotic episodes⁴. The treatment of steroid-induced psychosis is to taper or discontinue the steroid. Antipsychotics including haloperidol, chlorpromazine and risperidone were offered for the treatment of steroid-induced psychosis⁵.

This report is on an 11-year-old boy who was admitted

with TEN. After receiving a full-dose of steroids, he showed psychotic symptoms. We diagnosed him as steroid-induced psychosis. We tapered steroid and initiated an antipsychotic medication and intravenous immunoglobulin. Then his symptoms dramatically improved.

Case report

An 11-year-old boy was admitted to the department of pediatrics in our hospital with erythematous rashes over his entire body. The skin lesions started from face and neck, 3 days before admission and expanded to trunk and extremities. There were erythematous maculopapular rashes and multiple vesicles on the trunk and on legs. Targetoid lesions were observed at both palms and soles, accompanying severe pain.

About 8 weeks prior to this admission, he had been admitted to our hospital with his first episode of nephrotic syndrome. He had received high-dose steroid (Deflazacort: Calcort[®], 72 mg per day) for 8 weeks. Remission was achieved during induction therapy and by maintaining the use of steroids (Calcort[®], 24 mg per day).

He did not receive any other medication during the 8

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weeks before this episode of cutaneous eruptions, except for the Calcort[®], and had no history of known drug allergies. The patient denied any past psychiatric history, including depressive or manic symptoms. There was no family history of psychiatric illness.

On this visit to our center, the patient did not have any upper respiratory infection evidence like cough or rhinorrhea. His body temperature was 37.5°C, heart rate 72/min, respiratory rate 30/min and blood pressure 120/80 mmHg. During the physical examination, he had acute ill appearance with entire body covered with erythematous maculopapular rash. The neurological findings were negative with intact sensory and motor functions.

All laboratory tests including, white blood cell, hemoglobin, hemocrit, platelet, electrolytes, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine and albumin levels came out normal. The erythrocyte sedimentation rate was 11mm/H and C-reactive protein level was 0.415 mg/dL. The urinalysis findings were normal as well.

Investigation of the multiple vesicles located on the leg showed a negative Tzanck test and a negative Nikolsky's sign. Serologic tests for *Mycoplasma pneumoniae* and herpes simplex virus were negative. He had mild conjunctival injection but ophthalmological examination did not reveal any corneal lesions.

On the day of the admission, he was diagnosed with erythema multiforme and he was put on the schedule of maintained oral steroid (Calcort[®], 24 mg per day). He received conservative treatment for pain control, wet dressing and topical steroid ointment for skin lesions.

On the fourth day of hospitalization, skin lesion was getting worse with large bullae and positive Nikolsky's sign with severe pain.

On the eighth admission day, his skin lesions were diagnosed as toxic epidermal necrolysis (TEN) with skin erosion and large bullae on the entire body.

On the ninth day, high-dose intravenous steroid (Dexamethasone) was tried for the patient, but symptoms were intractable. On the following day, the patient developed aggressive and hostile personality and behavioral changes. He had psychotic symptoms with bizarre behavior, visual and auditory hallucination. When he closed his eyes, hallucinations appeared as a man trying to stab and torment him, and his mother was seen as the tormentor. He was unable to sleep.

We thus diagnosed him with steroid-induced psychotic disorder and decreased the amount of steroids and initiated a regimen of olanzapine (Zyprexa[®]). For the skin lesion, we tried intravenous immunoglobulin (IV-IG) 3g/kg for 3 days and supportive treatments were done. Because of his psychotic reaction and refractory to steroid in the skin lesion, we decided to start IV-IG.

Three days after starting the atypical antipsychotics drug, his symptoms were improved dramatically. The only side effect was mild sedation during daytime.

No abnormal findings were observed on urinalysis at any time during his stay in hospital. He was discharged after 22 days of hospitalization. His skin lesions were showing signs of recovery when he was released from the hospital.

Discussion

Toxic epidermal necrolysis (TEN) is a life-threatening idiosyncratic adverse drug reaction characterized by full thickness epidermal necrosis and eventual development of subepidermal bullae⁶⁾. To date, there are no validated tests to confirm the causative drug in these cases¹⁾. There is no particular treatment established for TEN⁷⁾.

The most commonly identified drugs are sulphonamide antibiotics, with rates of up to 4.5 cases per million users per week. Other antimicrobial agents include aminopenicillins, quinolones, cephalosporins, tetracyclines and imidazole antifungals. Frequent offenders also include anticonvulsant agents, non-steroidal anti-inflammatory drugs and allopurinol¹⁾. Roujeau et al.⁸⁾ reported that exposure to corticosteroids significantly increased the risk of SJS or TEN, although the exact mechanism is not known. This patient visited the hospital with skin lesions, erythematous maculopapular rash, and multiple vesicles on the trunk and legs. He was diagnosed with erythema multiforme (EM). It is known that *Mycoplasma pneumoniae* and herpes simplex virus are common cause of EM, but initial serologic tests were negative. He was put on the schedule of oral steroid therapy and he was tried NSAIDs for pain relief.

It is now known that many cytokines have been found in the involved epidermis. In particular, interleukin 6, tumor necrosis factor (TNF)-alpha and Fas ligand (FasL) have been shown to be highly expressed⁹⁾. Apoptotic keratinocytes become necrotic, and cohesion between adjacent keratinocytes and the basement membrane fails. The result is loss of epidermal viability and separation at the level of

the dermoepidermal junction¹).

The mortality of TEN is thought to be around 30%. The most common cause of death is infection, particularly involving *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida*¹⁰. In practice, on suspicion of a diagnosis, all potential causative agents should be discontinued; this often means that all drugs must be stopped. Immediate withdrawal of the attributable drug is known to improve prognosis¹¹. The most likely offending drug is one that has been newly administered within 4 weeks of presentation⁸.

Supportive therapy aims to limit the associated medical complications, which are the main cause of death. Rigorous adjustment of fluid, protein and electrolyte balance, strict thermoregulation, control of infection, and regular surveillance with sepsis screening are essential⁶.

Corticosteroids have been used to manage TEN for the last 30 years. Their use has been much debated and remains controversial. Proponents emphasize the importance of early intervention during the initial erythrodermic stage, with high doses for a few days only, to inhibit inflammation². However, there is considerable suggestion from previous studies that steroids may increase both morbidity and mortality as a consequence of increased risk of sepsis¹. Kim et al.⁷ reported a case of TEN caused by the use of steroid with enalapril in a child suffering from nephrotic syndrome. The reason for skin lesions not reappearing after oral deflazacort was changed to oral prednisolone after TEN remission, is not yet clear⁷.

The use of IV-IG with potent anti-Fas activity has been described previously in several case series for the treatment of TEN with inconsistent results¹¹. In the original pilot study, a series of 10 consecutive patients were treated with intravenous immunoglobulin at 0.2–0.75 g/kg for 4 days. In all patients, a rapid decrease in disease progression was seen, and all patients recovered¹². There are reports to suggest that plasmapheresis and haemodialysis may be used to remove the causative drug and its toxic metabolites from the circulation¹³. In this case, full-dose intravenous steroid was tried for the patient, and then he had psychotic symptoms with bizarre behavior, visual and auditory hallucination.

The psychiatric side effects of corticosteroids can include headache, insomnia, depression, and mood disorders (including bipolar and manic states) with or without psychotic episodes⁴. In an original report, Wada and colleagues¹⁴ described a case series of 18 patients (2,069 screened

patients) without prior psychiatric history, DSM-IV criteria for corticosteroid-induced psychotic or mood disorder, and symptoms persisting for at least 7 days. The prevalence of symptoms among referred cases was less than one percent, with 15 cases presented as mood disorders and 3 cases presented as psychotic disorder. The majority of patients demonstrated manic or bipolar symptoms and approximately half demonstrated psychotic features¹⁴.

Delirium is a serious neuropsychiatric disorder caused by a general medical condition or its treatment. It is characterized by an acute onset, fluctuating disturbances of consciousness, and cognitive disturbances¹⁵. The low cumulative incidence of 5% is mainly the result of the low incidence in the younger age groups (<9 year old). A clearly higher incidence is seen in the total sample (80%)¹⁶. In critically ill adult patients substantially higher incidences have been reported, ranging from 10–30% in general hospital setting to 50% in postoperative patients and up to 80% in the terminally ill¹⁵. The differential diagnosis of pediatric delirium consists of acute stress reactions, acute anxiety states, adjustment disorders with mixed emotions, dissociative and/or regressive states and childhood-onset psychosis¹⁶. Known risk factors are: severe illness, any medical procedure, exposure to medication, notably polypharmacy, malnutrition and dehydration¹⁵.

The time course of pain relief is consistent with reported onset of corticosteroid induced psychiatric symptoms⁴. It seems that higher doses of steroid predispose individuals to suffer from psychiatric episodes, although it is unclear if the dose impacts the development of psychosis specifically. From available evidence, the dose does not seem to affect the rate of onset, duration, or severity¹⁷.

Psychiatric symptoms have also been reported and these can vary from mild mood changes to full blown psychosis. Despite the lack of reports in the pain literature, the current case emphasizes the potential of corticosteroid induced psychosis following multiple interventional pain procedures performed in one session⁴.

Whenever delirium was identified or suspected, a two-track treatment approach consisting of both psychosocial and pharmacological interventions was implemented¹⁶. The treatment of steroid-induced psychosis is to taper the steroids to the lowest dose or to discontinue the medication⁵. In this case, corticosteroid had to be reduced to lower dosage because of concomitant use of IV-IG. Lithium and antipsychotics including haloperidol, chlorpromazine and

risperidone were offered for the treatment of steroid-induced psychosis⁵⁾. Atypical and typical antipsychotics are comparable in their clinical efficiency to some extent, but they differ remarkably in regards to their side effect profiles. Typical antipsychotics have more risk for developing extrapyramidal side effects (EPS) including dyskinesias and dystonias than atypicals⁵⁾. Purdon et al.¹⁸⁾ found a greater cognitive benefit with olanzapine relative to haloperidol and risperidone. This also describes a significantly greater proportion of patients taking haloperidol (73.3%) required anticholinergic treatment relative to risperidone (45%) and olanzapine (15%).

Children with nephrotic syndrome often experience serious problems with depression, anxiety and increased aggression during high-dose prednisone therapy¹⁹⁾. Lopez-Medrano et al.²⁰⁾ reported that higher levels of free and active fraction of steroids along with low plasma albumin levels will expose the patient to more adverse effects. However, steroid-induced psychosis was developed during remission of nephrotic syndrome in this patient.

In conclusion, an 11-year-old boy was admitted with TEN and he had been diagnosed as nephrotic syndrome already. Remission was achieved during induction therapy and by maintaining the use of steroids. After full-dose intravenous dexamethasone for TEN, he showed psychotic symptoms. We diagnosed him as having steroid-induced psychotic disorder. We reduced the amount of steroid and initiated an antipsychotic medication and IV-IG. Then his symptoms dramatically improved and he was discharged.

요 약

신증후군 환아에서 발생한 독성표피괴괴사용해 치료를 위해 사용된 고용량 스테로이드로 인한 정신질환 1례

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독성표피괴괴사용해(TEN)와 스티븐-존슨 증후군(SJS)은 약물이나 감염에 의해 발생하는 피부점막을 침범하는 드물지만 치명적인 질병이다. 스테로이드는 TEN의 치료에 많이 이용되어왔지만, 아직까지도 논쟁중이다. 스테로이드에 의한 정신과적 영향은 두통, 불면증, 우울증, 심리질환 등이 있다. 스테로이드에 의한 정신질환에서 치료는 스테로이드의 감량 또는 중단이고, 항정신성 약물을 투여한다. 신증후군으로 진단된 11세 남아에서 스테로이

드 치료 후 관해상태에서 유지치료를 시행하고 있던 중에 TEN이 발생하였다. 저자들은 이 환아에서 치료목적으로 투여한 고용량 스테로이드 정맥주사로 인해 정신질환이 동반되었고, 이후 스테로이드 감량과 항정신성 약물과 면역글로불린으로 증상이 호전되는 것을 경험하여 이를 보고하는 바이다.

References

- 1) Mukasa Y, Craven N. Management of toxic epidermal necrolysis and related syndromes. *Postgrad Med J* 2008;84:60-5.
- 2) Chave TA, Mortimer NJ, Sladden MJ, Hall AP, Hutchinson PE. Toxic epidermal necrolysis: current evidence, practical management and future directions. *Br J Dermatol* 2005;153:241-53.
- 3) Lauerma AI, Reitamo S, Maibach HI. Systemic hydrocortisone/cortisol induces allergic skin reactions in presensitized subjects. *J Am Acad Dermatol* 1991;24:182-5.
- 4) Benyamin R, Vallejo R, Kramer J, Rafeyan R. Corticosteroid induced psychosis in the pain management setting. *Pain Physician* 2008;11:917-20.
- 5) Hergüner S, Bilge I, Yavuz YA, Tüzün DU. Steroid-induced psychosis in an adolescent: treatment and prophylaxis with risperidone. *Turk J Pediatr* 2006;48:244-7.
- 6) Revuz J, Roujeau JC, Guillaume JC, Penso D, Touraine R. Treatment of toxic epidermal necrolysis. *Arch Dermatol* 1987;123:1156-8.
- 7) Kim DW, Jung DE, Koo JW. Steroid and enalapril therapy—possible cause of toxic epidermal necrolysis. *Korean J Pediatr* 2006;49:332-6.
- 8) Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995;333:1600-7.
- 9) Werhli P, Viard I, Bullani R, Tschopp J, French LE. Death receptors in cutaneous in cutaneous biology and disease. *J Invest Dermatol* 2000;115:141-8.
- 10) Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994;331:1272-85.
- 11) Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: The University of Miami Experience. *Arch Dermatol* 2003;139:39-43.
- 12) 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.
- 13) Kamanabroo D, Schmitz-Landgraf W, Czarnetzki BM. Plasmapheresis in severe drug-induced toxic epidermal necrolysis. *Arch Dermatol* 1985;121:1548-9.
- 14) Wada K, Yamada N, Sato T, Suzuki H, Miki M, Lee Y, et al. Corticosteroid -induced psychotic and mood disorders: diagnosis defined by DSM-IV and clinical pictures. *Psychosomatics* 2001;42:461-6.
- 15) Schievelde JN, Lousberg R, Berghmans E, Smeets I, Leroy PL, Vos GD, et al. Pediatric illness severity measures predict

- delirium in a pediatric intensive care unit. *Crit Care Med* 2008;36:1933-6.
- 16) Schieveld JN, Leroy PL, van Os J, Nicolai J, Vos GD, Leentjens AF. Pediatric delirium in critical illness: phenomenology, clinical correlates and treatment response in 40 cases in the pediatric intensive care unit. *Intensive Care Med* 2007;33:1033-40.
 - 17) Clark LD, Bauer W, Cobb S. Preliminary observations on mental disturbances occurring in patients under therapy with cortisone and ACTH. *N Engl J Med* 1952;246:205-16.
 - 18) Purdon SE, Jones BD, Stip E, Labelle A, Addington D, David SR, et al. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. *Arch Gen Psychiatry* 2000;57:249-58.
 - 19) Soliday E, Grey S, Lande MB. Behavioral effects of corticosteroids in steroid-sensitive nephrotic syndrome. *Pediatrics*. 1999;104:e51.
 - 20) Lopez-Medrano F, Cervera R, Trejo O, Font J, Ingelmo M. Steroid induced psychosis in systemic lupus erythematosus: a possible role of serum albumin level. *Ann Rheum Dis* 2002;61:562-3.