□ Case Report □

# A case of dapsone syndrome

Yoo Jong Won, M.D., Ok Lan Kim, M.D., Seung Taek Yu, M.D.
Young Wook Yoon, M.D. and Du Young Choi, M.D.

Department of Pediatrics, School of Medicine, Wonkwang University, Iksan, Korea

Diamino-diphenyl-sulfone (Dapsone) is widely used in the treatment of leprosy and a variety of blistering skin diseases. It sometimes has adverse side effects with common usual doses, such as skin, nervous system, gastrointestinal tract, liver, kidney and hematologic toxicity. One of these side effects is a rare but serious hypersensitivity reaction called dapsone syndrome, which occurs several weeks after the initial administration of the drug and results in unpredictable, sometimes fatal outcomes. This report deals with a 13-year-old girl's case with typical features of dapsone syndrome that included fever, exfoliative dermatitis, jaundice, hemolytic anemia and pleural effusion after being treated with dapsone for four weeks. **(Korean J Pediatr 2007;50:493-496)**

**Key Words :** Dapsone syndrome, Hemolytic anemia

## Introduction

Dapsone has been used for leprosy, various skin diseases, malaria, and *Pneumocystis carinii* pneumonia in AIDS patients because of its potent antibiotic and anti-inflammatory effects[1-3]. Dapsone therapy may cause a variety of adverse effect including hematologic, hepatic and dermatologic toxicity. One of these reactions called dapsone syndrome is characterized by high fever, hepatitis, exfoliative dermatitis, lymphadenopathy and hemolytic anemia occurring within 3-6 weeks after starting on dapsone treatment [4-6]. There have been 4 reported cases of this syndrome including a case for a child in Korean literature[7-9].

We here report a case of dapsone syndrome occurring after receiving 100 mg of dapsone for 4 weeks to cure a chronic skin disease. Initially she showed typical clinical features of this syndrome with pleural effusion, and progressively improved after stopping dapsone and administering prednisone without any sequelae.

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책임저자 : 최두영, 원광대학교 의과대학 소아과학교실
Correspondence : Du Young Choi, M.D.
Tel : 063)850-1104 Fax : 063)853-3670
E-mail :cdy8118@wonkwang.ac.kr

## Case Report

A 13-year-old girl was referred to our hospital because of fever, jaundice, pallor face and pruritic skin rash lasting for 3 days. She has suffered from a chronic skin disease for eight years and has been administered 100 mg/day of dapsone, 400 mg/day of cimetidine, and 50 mg/day of ascorbic acid during the last four weeks at the other hospital before the referral. There was mild epigastric pain but no clay-colored stools. The vital signs were stable. The result of a physical examination was unremarkable except enlarged liver (8 cm below costal margin in midclavicular line). The skin showed erythematous maculopapular rash all over the body with predominant involvement of face and lower extremities. There was no edema of face or limbs (Fig. 1A, 1B).

On admission, a complete blood count revealed hemoglobin 8 g/dL, hematocrit 24.6%, white cell count 13,110/$mm^3$ (neutrophils 63.6%, lymphocytes 25.1%, eosinophils 2.5%), platelet count 257,000/$mm^3$ and the erythrocyte sedimentation rate was 4 mm/hr. Peripheral blood smear showed normocytic normochromic anemia with bite cells, toxic granules, and vacuoles. The corrected reticulocyte count was 10.34%. The direct and indirect Coombs test were negative. Liver function tests were as follows: total bilirubin 6.77 mg/dL with a direct of 4.62 mg/dL, AST 182.4 IU/L, ALT 334 IU/L, alkaline phosphatase 423.5 IU/L, LDH 1,837 IU/L,

serum albumin 3.11 g/dL. Serological test for hepatitis A virus, hepatitis B virus, hepatitis C virus, Epstein-Barr virus, cytomegalovirus and mycoplasma pneumoniae were negative. Autoimmune markers (ANA, ANCA) were also negative. Abdominal ultrasonography showed hepatosplenomegaly, thickening of the gallbladder wall and small amount of ascites without any evidence of biliary obstruction.

Antihistamines, antipyretics and broad-spectrum antibiotic were empirically administered with a cessation of dapsone at the time of admission. On the third hospital day, edema appeared on both hands and feet and gradually deteriorated to oliguria, generalized edema, pleural effusion with an albumin of 2.60 g/dL. Microscopic examination of the skin biopsy on face showed dermatitis with some apoptotic keratinocytes, suggesting cytotoxic drug eruption (Fig. 2A, 2B). With a diagnosis of dapsone syndrome, prednisolone 90 mg/day was prescribed with fluid restriction, diuretics and albumin administration for edema. Her clinical condition quickly improved, and the results of subsequent laboratory test gradually returned to normal level within 2 weeks. Prednisolone was carefully tapered over 1 month to minimize recurrence.

## Discussion

Dapsone (Diamino-Diphenyl-sulfone) is the parent compound of the sulfones. It was first synthesized in 1908, though its antibacterial properties were recognized in 1937[10]. The drug has been used as a first-line treatment of leprosy and employed to treat dermatitis herpetiformis, other dermatologic conditions and *Pneumocystis carinii* infection for over 40 years[1-3]. It gets absorbed rapidly into the gastrointestinal tract and transported through the portal circulation to the liver, where it mainly is metabolized by N-acetylation and N-hydroxylation. It is eliminated primarily in urine and partly in enterohepatic circulation[11].

Although dapsone infrequently causes adverse reactions at normal dose, which is less than 100 mg per day, several

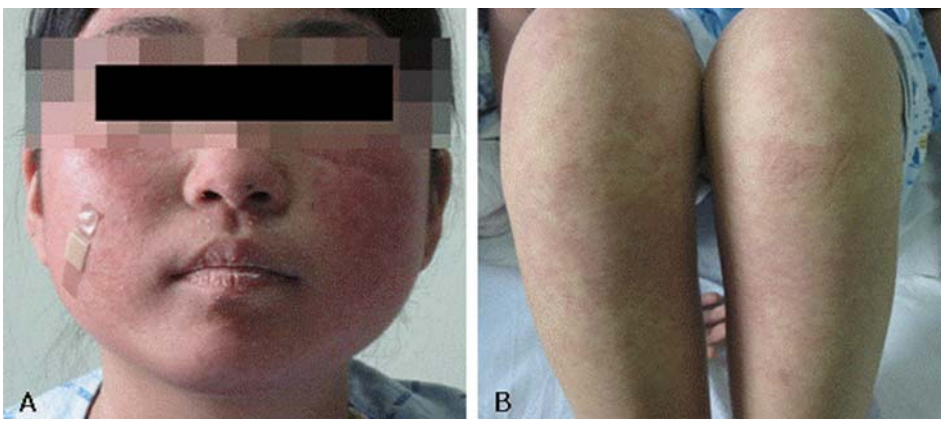


**Fig. 1.** Patient's photography shows erythematous, exofoliative maculopapules on the edematous face (A) and polymorphic erythematous maculopapules disseminated on lower extremities (B).

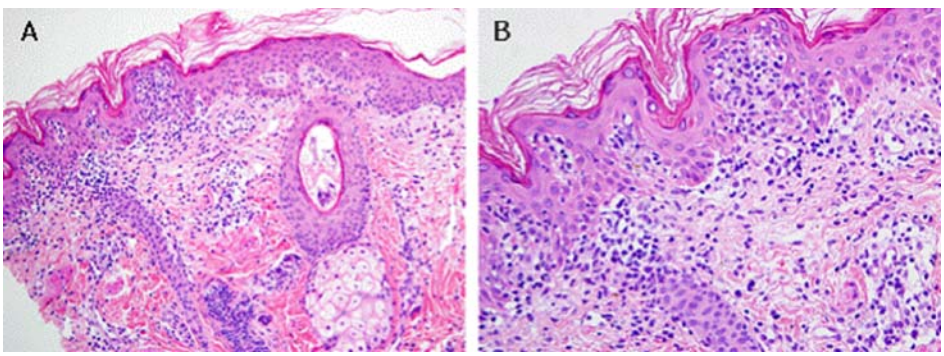


**Fig. 2.** Histopathologic finding of skin lesion represents inflammatory cell infiltration in perivascular areas of the upper dermis (H&E stain, A: ×200, B: ×400).

side effects have been reported. It may cause skin, nervous system, gastrointestinal tract, liver, kidney and hematologic toxicity[4-6]. The most common side effects are the dose-dependent hematologic problems such as methemoglobinemia and hemolytic anemia, which is mainly caused by the potent oxidant, hydroxylamine and other hydroxylated metabolites. Also, some other serious and unpredictable hematologic side effects, agranulocytosis and the dapsone hypersensitivity syndrome called dapsone syndrome can occur, though rarely.

Dapsone syndrome has a frequency of 0.2-0.5% in patients on drug therapy, and it typically begins within several weeks of starting on the drug[12-14]. It can be a manifestation of the so-called DRESS syndrome (drug rash with eosinophilia and systemic symptoms), which is a serious condition that has been reported in association with various drugs, such as anticonvulsants, sulfonamides, allopurinol, minocycline and gold salts[15]. Although the pathogenesis of this syndrome is not clear, findings from positive lymphocyte stimulation tests and predominantly activated cytotoxic T cells in the dermis of patients with this syndrome suggest an allergic rather than an idiosyncratic reaction[16]. The predominant manifestations of this syndrome consist of fever, exfoliative dermatitis, lymphadenopathy, lymphocytosis, methemoglobinemia, hemolytic anemia and hepatotoxicity. The rash initially begins as a benign morbilliform eruption, and progresses into frank exfoliative dermatitis. Liver involvement displays a mixed hepatocellular and cholestatic pattern[4, 11, 15]. The principal treatment of this syndrome is a cessation of drug therapy and administration of corticosteroid although there has been no double blind studies on the effectiveness of corticosteroid. The prednisolone in the range of 30 to 60 mg per day may be given and should be cautiously tapered off to prevent recurrence. Since dapsone can remain in the affected organs up to 35 days due to protein binding and enterohepatic circulation, tapering of prednisolone over a period of about one month is required[4]. This syndrome is generally self-limiting, but it could be fatal if left untreated[17].

Our case had typical features of dapsone syndrome. Her symptoms appeared within four weeks of starting on dapsone. She had fever and exfoliative dermatitis, methemoglobinemia. Hemolytic anemia was also present as evidenced by low hemoglobin, high reticulocyte count, suggestive peripheral blood picture, and a high bilirubin. Progressive edema and pleural effusion present in the patient were caused by hypoalbuminemia, which is probably due to binding of dapsone to the circulating serum albumin.

Here, we dealt with a case of dapsone syndrome with typical manifestations which developed after using 4 weeks of dapsone. With recent increase in the usage of dapsone in chronic skin diseases, physicians should be aware of this syndrome when treating patients with fever, skin rash, and jaundice.

## 한 글 요 약

### Dapson 증후군 1례

*원광대학교 의과대학 소아과학교실*

**원유종, 김옥란, 유승택, 윤영욱, 최두영**

Dapsone은 나병과 여러 수포성 피부 질환의 치료에 널리 사용되고 있다. 일반적인 투여 용량의 dapsone은 부작용이 드물지만, 피부, 신경계, 위장관, 간, 신장과 혈액학적 합병증을 일으킬 수 있다. 이들 부작용 중 하나인 dapsone 증후군은 약물 투여 수주 후에 발생하여, 예측 불가능하게 진행하며 치명적인 경과를 취할 수 있는 중증 약물 과민 반응이다. 저자들은 dapsone 투여 4주 후에 열, 박탈성 피부염, 황달, 용혈성 빈혈, 늑막 삼출 등의 특징적인 임상 소견을 보인 dapsone 증후군 1례를 경험하였기에 보고하는 바이다.

## References

1) Bernstein J, Lorincz A. Sulfonamides and sulfones in dermatologic therapy. Int J Dermatol 1981;20:81-8.
2) Chiodini P. The chemoprophylaxis of malaria. J Antimicrob Chemother 1987;2:297-302.
3) Mills J, Leoung G, Medina I, Hopewell PC, Hughes WT, Wofsy C. Dapsone treatment of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. Antimicrob Agents Chemother 1988;32:1057-60.
4) Prussick R, Shear NH. Dapsone hypersensitivity syndrome. J Am Acad Dermatol 1996;35:346-9.
5) Wolf R, Matz H, Orion E, Tuzun B, Tuzun Y. Dapsone: unapproved uses or indications. Clin Dermatol 2000;18:37- 53.
6) Tomecki KJ, Catalano CJ. Dapsone hypersensitivity. The sulfone syndrome revisited. Arch Dermatol 1981;117:38-9.
7) Kim JW, Kim JS. Two Cases of Dapsone Syndrome. Korean J Dermatol 2005;43:655-9.
8) Choi HW, Song IK, Chung EA, Cha DY, Lim MK, Na DJ, et al. A case of Sulfone syndrome hypersensitivity associated with dapsone. J Asthma Allergy Clin Immunol 2001; 21:1206-10.
9) Seoh JK, Bae HK, Yang JS, Choi ED, Lim BK, Kim JS. A Case of Dapsone Syndrome. J Korean Pediatr 1988;31:1376-80.
10) Lowe J. Treatment of leprosy with diamino-diphenyl sul-

phone by mouth. Lancet 1950;1:145-50.
11) Zuidema J, Hilbers-Modderman ES, Merkus FW. Clinical pharmacokinetics of dapsone. Clin Pharmacokinet 1986;11: 299-315.
12) Puri AS, Gupta R, Ghoshal UC, Khan E, Aggarwal R, Naik SR. Hepatic injury in sulfone syndrome: hepatitis or cholestasis? Indian J Gastroenterol 1995;14:20.
13) Allday EJ, Barnes J. Toxic effects of diaminodiphenyl-sulphone in the treatment of leprosy. Lancet 1951;2:205-6.
14) Ghislain PD, Roujeau JC. Treatment of severe drug reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. Dermatol online J 2002; 8:5.
15) Gruchalla RS. Drug allergy. J Allergy Clin Immunol 2003; 111(2suppl):548-59.
16) Saito S, Ikezawa Z, Miyamoto H, Kim S. A case of the 'dapsone syndrome'. Clin Exp Dermatol 1994;19:152-6.
17) Kumar RH, Kumar MV, Thappa DM. Dapsone syndrome-a five year retrospective analysis. Indian J Lepr 1998;70:271-6.