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CASE REPORT

Dapsone Hypersensitivity Syndrome That Occurred during Treatment of Pediatric Patient with Erythema Elevatum Diutinum

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Herein, we report a case of an 8-year-old girl with dapsone hypersensitivity syndrome (DHS) that occurred during the treatment of erythema elevatum diutinum. She had fever, gross hematuria, and malaise for three weeks after initiation of dapsone therapy. Five days after stopping dapsone treatment, she returned to the emergency clinic because of high fever, emesis, diarrhea, upper respiratory symptoms, and worsening of exanthematous eruptions. A diagnosis of DHS was made, and it improved with oral prednisone. We recommend that pediatric patients who are treated with dapsone need to be observed carefully for the development of DHS. **(Ann Dermatol 23(S3) S290～S295, 2011)**

-Keywords-
Dapsone, Drug hypersensitivity syndrome, Erythema elevatum diutinum

INTRODUCTION

Dapsone is indicated for the treatment of leprosy, but it is also used for various skin diseases[1]. Moreover, dapsone is the drug of choice for the management of erythema elevatum diutinum (EED)[2]. The most frequent associated side effects are dose-related hemolytic anemia and methaemoglobinemia[2]. More rarely, dapsone can cause severe adverse effects, such as dapsone hypersensitivity syndrome (DHS) or agranulocytosis[1]. DHS typically starts within eight weeks of initiating dapsone treatments and is characterized by fever, rash, hemolytic anemia, lymphocytosis and hepatitis[1,3]. Herein, we report DHS that occurred during the treatment of a pediatric patient with EED.

CASE REPORT

An 8-year-old girl presented with tender papules and nodules on the extensor surfaces of the extremities that had been there for seven months. A physical examination revealed firm, erythematous to skin-colored papules and nodules on her both hands, wrist, feet, elbows, and knees (Fig. 1). The histopathologic examinations of the skin lesions from her hand revealed widespread vasculitis in the small vessels of the dermis with fibrinoid deposits and extravasated red blood cells. The infiltrates were composed of multiple small aggregates of histiocytes, neutrophils, and nuclear fragments (Fig. 2). Thus, the clinical and histopathological findings were consistent with a diagnosis of EED.

Despite several months of potent topical and systemic steroid therapy, the cutaneous lesions remained, and she was started on dapsone treatment. The dosing regimen of dapsone consisted of taking 100 mg daily for two days and skipping for one day. A dramatic and rapid response was seen within two weeks of initiation of dapsone therapy.

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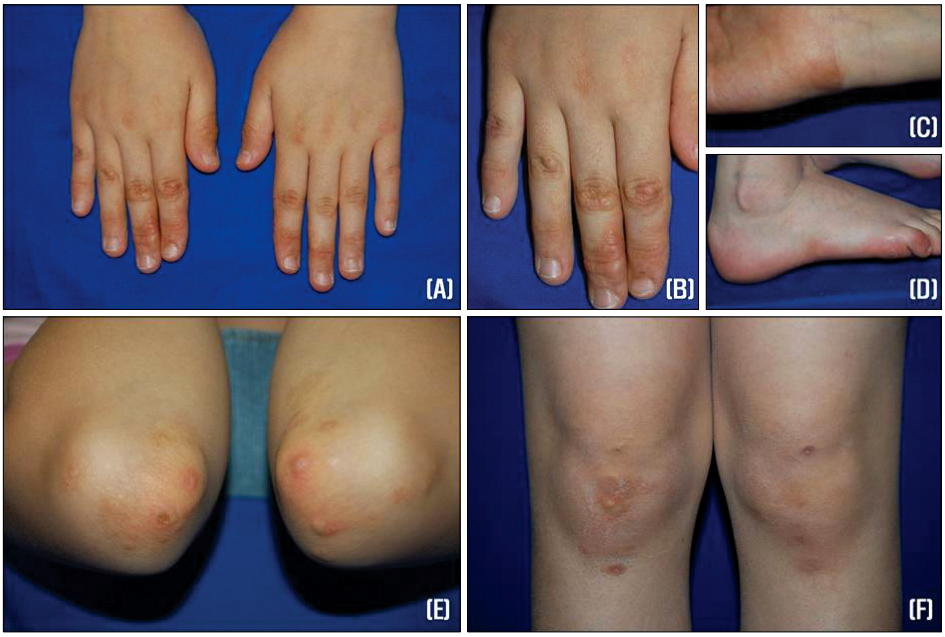

Fig. 1. (A) Multiple, persistent, symmetric and erythematous to skin-colored papules and nodules on the extensor surfaces of the hands. (B) Close up view of the right hand, (C) right wrist, (D) right foot, (E) elbows and (F) knees.

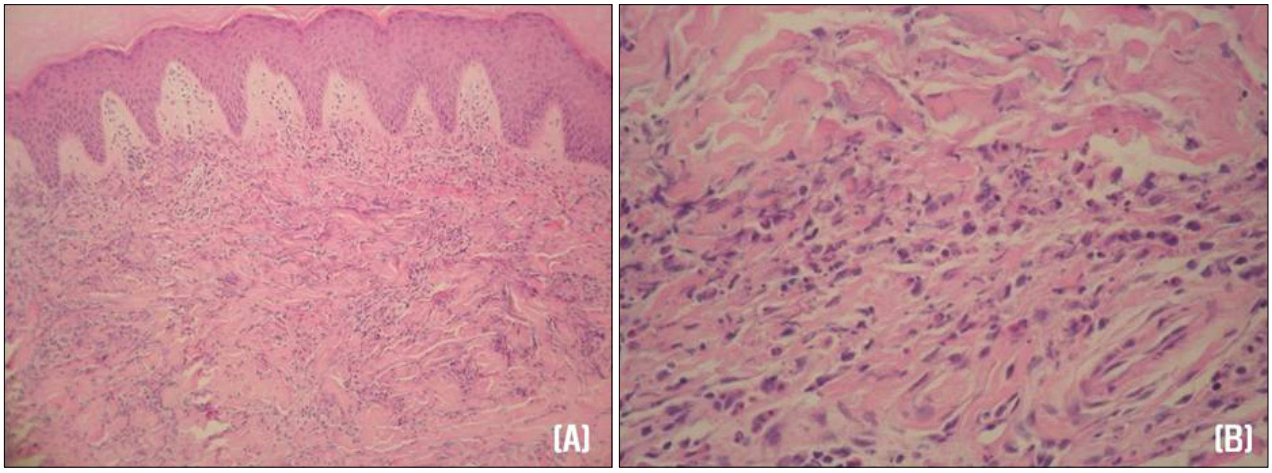

Fig. 2. (A) Biopsy of an early lesion from the hand revealed widespread vasculitis in the small vessels of the dermis with fibrinoid deposits and extravasated red blood cells (H&E, ×100). (B) The infiltrates were composed of multiple small aggregates of histiocytes, neutrophils, and nuclear fragments (H&E, ×400).

However, she stopped the dapsone treatment after three weeks of treatment due to gross hematuria, malaise, fever, and cough. At that time, she was thought to have a viral illness or an unrelated upper respiratory infection. Nevertheless, five days after stopping treatment of dapsone, she returned to the emergency clinic because of high fever, emesis, diarrhea, upper respiratory symptoms, and a worsening rash. She also had maculopapular exanthematous eruptions with facial edema and lymphadenopathies (Fig. 3). She was hospitalized, and blood samples were taken for routine examination, including viral serology, bacterial culture, complement levels, and autoimmune screening.

A complete blood count revealed a hemoglobin of 9.7 mg/dl, a hematocrit of 31.0, a white blood cell count of 30,110/mm^3, reticulocyte count of 5.74%, a platelet count of 124,000/mm^3, and a C-reactive protein of 0.51 mg/dl in the first hour. Her liver function tests were abnormal: aspartate aminotransferase 441 U/L, alanine aminotransferase 657 U/L, alkaline phosphatase 1,023 U/L, total bilirubin 6.06 mg/L, direct bilirubin 3.88 mg/dl, prothrombin time 16.2 seconds, international normalized ratio 1.35, partial thromboplastin time 43.0 seconds, and lactate dehydrogenase 2,221 U/L. Titers were negative for viral hepatitis serology (hepatitis A, B, and C) and Epstein-Barr

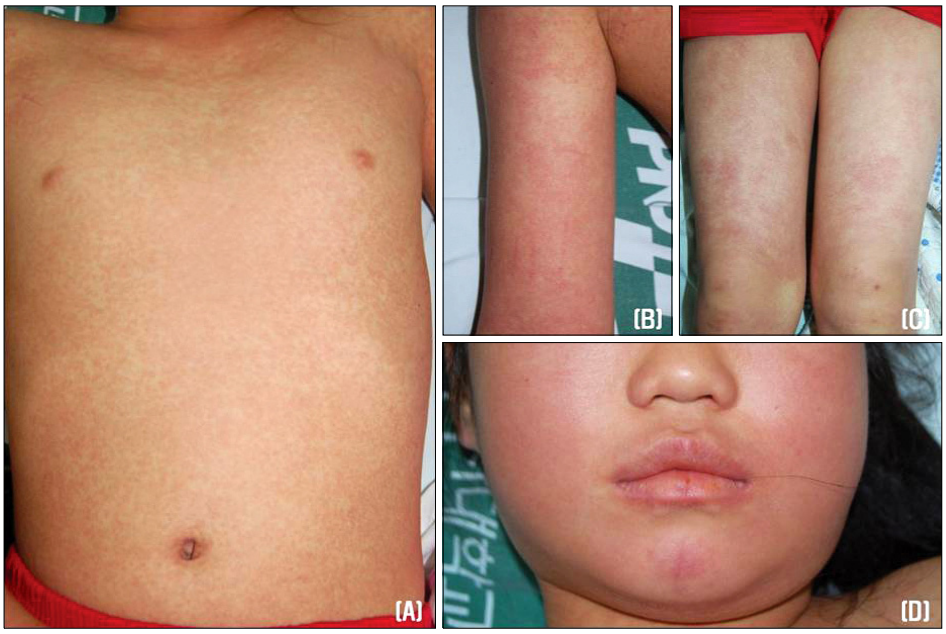

Fig. 3. Symmetrically arranged, brightly erythematous macules and papules on trunk (A), arms (B), legs (C) and face with edematous swelling (D).

virus. Although there was gross hematuria, the levels for urea, creatinine, and electrolyte in the blood were within normal limits. Bacterial cultures (blood and urine), levels of complement (C3, C4, and CH50), and autoimmune screen (antinuclear antibody) were all negative or within normal limits.

A diagnosis of DHS was made, and the patient was treated with oral prednisone (60 mg/day). Her condition improved quickly and laboratory test results returned to normal levels within two weeks.

DISCUSSION

EED is a chronic recurrent form of cutaneous leukocytoclastic vasculitis thought to be immune-complex mediated[4,5]. It typically presents as multiple, persistent, symmetric and erythematous to violaceous papules/plaques on the extensor surfaces of the extremities[4,5]. The histopathologic features characteristic of EED are not usually all present within the same lesion[5]. A spectrum from leukocytoclastic vasculitis to vessel occlusion and dermal fibrosis are observed[5]. Early stage lesions are characterized by neutrophilic, perivascular infiltrates with dermal fibrin deposits, endothelial expansion, and leukocytoclasis[5,6]. With disease progression, a granulation tissue-like response with dermal fibrosis and capillary proliferation become the predominant features[5,6]. Diagnosis of EED must be based on a characteristic clinical presentation and confirmatory histopathological findings[5,6].

Dapsone has been broadly used for treatment of leprosy and a wide variety of dermatological inflammatory diseases because of its excellent anti-inflammatory and immunomodulatory effects[1]. Generally, dapsone or sulfonamides are considered to be a first-line treatment for EED[5,6]. The responsiveness of EED to dapsone is thought to be secondary to its inhibitory effects on neutrophil chemotaxis and function[2]. Therefore, we tried dapsone therapy in our patient, because her lesions did not respond to topical and systemic steroids. Although a dramatic and rapid response was seen within two weeks of initiation of therapy, DHS occurred three weeks after initiation of dapsone therapy.

The most frequent side effects of dapsones are dose-related methemoglobinemia and hemolytic anemia, and rarely, it can cause an idiosyncratic reaction, called dapsone hypersensitivity syndrome[1-3]. DHS has been reported for a variety of dermatological conditions, including leprosy, dermatitis herpetiformis, acne vulgaris, psoriasis, leukocytoclastic vasculitis, cicatrical pemphigoid, pemphigus and lupus erythematosus[1,3].

A true diagnosis of DHS should be made based on the following criteria: 1) symptoms manifesting within eight weeks of starting therapy and resolving after withdrawal of the drug, 2) symptoms not attributable to any other drug used simultaneously, and 3) symptoms unrelated to leprosy or any underlying disease[7,8].

DHS is a severe, multiorgan reaction to dapsone that includes fever, rash, jaundice, lymphadenopathy, splenomegaly and pedal edema[1,3]. Hemolytic anemia, atypical lymphocytosis and hepatitis are other accompanying findings[1,3]. Of note, fever almost invariably presents as the initial sign[9]. In addition, prominent edema of the face,

particularly in the periorbital area, is a noticeable feature of drug induced hypersensitivity syndrome[9]. The rash, which is often initially a benign morbilliform eruption, may develop into exfoliative dermatitis[1,3].

Our patient showed consistent clinical and laboratory findings of DHS and her symptoms appeared within three weeks of starting on dapsone. In particular, it is noteworthy that hemolytic anemia was also present, as proved by decreased hemoglobin, high reticulocyte count, and high bilirubin. In addition, it is essential to check levels of enzyme glucose 6-phosphate hydrogenase (G6PD) before beginning dapsone, because G6PD-deficient patients may

Table 1. Reported cases of dapsone hypersensitivity syndrome in the Korean literature

Case number	1	2	3	4	5	6	7
Author	Choi et al.[18]	Kim and Kim[19]	Kim and Kim[19]	Lim et al.[20]	Won et al.[21]	Lee et al.[22]	Our case
Age (yrs)/Gender	62/F	23/M	52/M	59/F	13/F	47/F	8/F
Primary disease	Arthralgia	Hand eczema	Rheumatoid arthritis	Recurrent oral ulcer	Chronic skin disease	Behcet disease	Erythema elevatum diutinum
Dose of dapsone (mg/day)	100	100	100	50～100	100	100	67
Duration of therapy before DHS (weeks)	4	2	3	6	4	3	3
Fever	−	+	+	+	+	+	+
Rash	Maculopapules	Maculopapules, pustules	Maculopapules	Maculopapules	Maculopapules	Maculopapules	Maculopapules
Lymphadenopathy	−	+	+	+	−	+	+
White blood cells (normal: $<11,000/mm^3$)	8,740	13,300	15,000	21,500	13,110	10,100	31,110
Total eosinophils (normal: $<600/mm^3$)	8.1%	7%	9%	3%	2.5%	15.2%	3.5%
Hemoglobin (normal male: >12.3; female: >11.3 g/dl)	9.9	None	None	7.4	8.0	7.7	9.7
C-reactive protein (normal: <0.8 mg/dl)	None	2.53	2.24	None	−	107	0.51
Albumin (normal: >3.5 g/dl)	3.5	None	None	2.1	3.11	2.6	3.5
Total bilirubin (normal: >1.2 mg/dl)	0.8	1.4	None	16.07	6.77	13.2	6.06
Aspartate aminotransferase (normal: <37 U/L)	88	1,996	567	561	182.4	3,224	441
Alkaline aminotransferase (normal: <41 U/L)	84	3,416	345	608	334	2,703	657
Alkaline phosphatase (normal: <220 U/L)	240	290	340	287	423.5	534	1,023
Systemic therapy	Systemic steroids	Systemic steroids, antihistamines	Systemic steroids, antihistamines	Systemic steroids, immuno-globulins	Systemic steroids	Systemic steroids	Systemic steroids

F: female, M: male, DHS: dapsone hypersensitivity syndrome.

experience severe hemolysis[1-3].

It is presumed in the pathogenesis of DHS that hypersensitivity to dapsone may be caused by metabolites of dapsone-forming haptens with the formation of anti-dapsone antibodies[10,11]. The exact incidence of DHS is not known, but it is reported to occur in less than 1% of patients treated with dapsone[1,3]. According to a study by Agrawal and Agarwalla[3], the mean age in patients with DHS was 33.2 years (range 13 to 64 years). Although aging was a relatively adverse predisposing factor for side effects of daponse[1], there was no higher predominance of DHS in pediatric patients. Most of the patients were below 50 years of age and this may be because of the decreased enzyme activity and production of toxic metabolites with aging[1].

Typically the symptoms of DHS begin within two to six weeks of the start of therapy (Table 1). However, it can appear as early as six hours in a previously sensitized individual or as late as six months after the start of dapsone therapy[12]. Due to its significant enterohepatic circulation, dapsone has a long elimination half-life that averages between 24 and 30 hours[13]. This is important to remember in case adverse reactions emerge after a long metabolite impact period[14]. The initial dosage is crucial in DHS, and Labandeira and Toribio[15] suggest that a high dose (>50 mg/day) in the first six to eight weeks of treatment is advisable in patients who do not have leprosy. A mortality rate of 11~13% has been reported, and hepatic encephalopathy is prominent in fatal cases[16].

DHS is generally a self-limiting drug reaction, and most patients recover following cessation of dapsone therapy[14]. However, a systemic corticosteroid is frequently used in its treatment. The duration of recovery has been shown to be shorter in patients who received a systemic corticosteroid, although no controlled studies have been performed to evaluate it effectiveness[1,3].

To our knowledge, there has been one reported case of DHS occurring in patients with EED. Potter et al.[17] reported the case of a 68-year-old man with EED who had been taking dapsone, 200 mg/day, and developed DHS three weeks after commencement of the drug. In fact, it is unclear whether EED itself affects DHS, because this case is the second case of DHS during treatment of EED. However, the use of dapsone is recently decreasing in dermatologic inflammatory disease because of the reduction of leprosy patients and development of new drugs. Moreover, it is difficult to find any dermatologic diseases for which dapsone is recommended as first line treatment. In this regard, it is highly suggestive that dapsone or sulfonamides are still considered a first-line treatment for EED. Since treatment of EED remains challenging due to the chronic and recurrent nature of the disease, dapsone was necessary to use in our patient for the treatment of EED.

In conclusion, we emphasize that more attention is needed for dapsone therapy in the patient with EED. In addition, physicians, especially those prescribing drugs for pediatric patients, should be alert to this rare but potentially life-threatening adverse drug effect.

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