

# Severe Dapsone Hypersensitivity Syndrome

O Sener,<sup>1</sup> L Doganci,<sup>2</sup> M Safali,<sup>3</sup> B Besirbellioglu,<sup>4</sup> F Bulucu,<sup>5</sup> A Pahsa<sup>4</sup>

<sup>1</sup>Division of Allergy, <sup>2</sup>Department of Microbiology and Clinical Microbiology, <sup>3</sup>Department of Pathology, <sup>4</sup>Department of Infectious Diseases, and <sup>5</sup>Department of Internal Medicine Gulhane Military Medical Academy, Ankara, Turkey

**Abstract.** Dapsone, a potent antiparasitic and anti-inflammatory compound, is mainly used in the treatment of leprosy and a variety of blistering skin diseases. It may cause a severe adverse reaction with multiorgan involvement known as dapsone hypersensitivity syndrome. We report the case of a 21-year-old female patient with dapsone hypersensitivity syndrome. The clinical presentation mimicked a viral exanthema.

**Key words:** Dapsone hypersensitivity. Dermatitis herpetiformis.

**Resumen.** La dapsona, un potente compuesto antiparasitario y antiinflamatorio, se utiliza principalmente para el tratamiento de la lepra y diversas enfermedades cutáneas ampollosas. Puede causar una grave reacción adversa con afectación multiorgánica denominada síndrome de hipersensibilidad a la dapsona. Presentamos el caso de un paciente de 21 años de edad con síndrome de hipersensibilidad a la dapsona. Las manifestaciones clínicas imitaron las de un exantema vírico.

**Palabras clave:** Hipersensibilidad a la dapsona. Dermatitis herpetiforme.

## Introduction

Dapsone (4, 4'-diamino-diphenyl sulfone), a potent anti-inflammatory and antiparasitic compound, is still used as a first line drug for leprosy. In Europe and the United States of America, however, it finds application mainly in the treatment of bullous dermatoses and dermatitis herpetiformis [1]. The most frequent side effects are dose-related methemoglobinemia and hemolytic anemia, and rarely, it can cause an idiosyncratic reaction, called dapsone hypersensitivity syndrome (DHS). We report the case of a woman with DHS mimicking a viral exanthema.

## Case Description

A 21-year-old white Turkish woman was referred to our infectious diseases clinic with suspicion of severe measles or infectious mononucleosis. Her chief complaints were high fever lasting for 4 days associated with malaise, sore throat, dysphagia, productive cough, and a pruritic rash. She reported having no important health problem until intense pruritus started 6 months

earlier. She was given a diagnosis of dermatitis herpetiformis based on a skin biopsy, and she was given oral dapsone 100 mg/day by a dermatologist elsewhere. She developed cyanosis on her lips, fingers, and toes within a week of starting therapy. Dapsone-induced methemoglobinemia was diagnosed and therapy was stopped. Four weeks later, she consulted her primary care physician with complaints of high fever, malaise, lymphadenopathy, maculopapular skin rash, and painful oral mucosal lesions. She was referred to our infectious diseases clinic with a suspected diagnosis of adult rubeola infection or infectious mononucleosis.

On admission, her temperature was 40°C, blood pressure was 100/60 mm Hg, and heart rate was 112 beats/min. She had bilateral conjunctivitis, periorbital edema, and a pruritic maculopapular exanthematous rash with pustules over her forehead, neck, trunk, back, and extremities (Figure 1). Multiple bilateral cervical and retroauricular lymph nodes measuring 1 to 2 cm and tender were noted. She had a 4-cm slightly tender enlarged liver below the costal margin. There was no splenomegaly or ascites. Her pharynx was hyperemic, and she had Stevens-Johnson-like lesions in the oral cavity. Lung and heart sounds were unremarkable except for slight

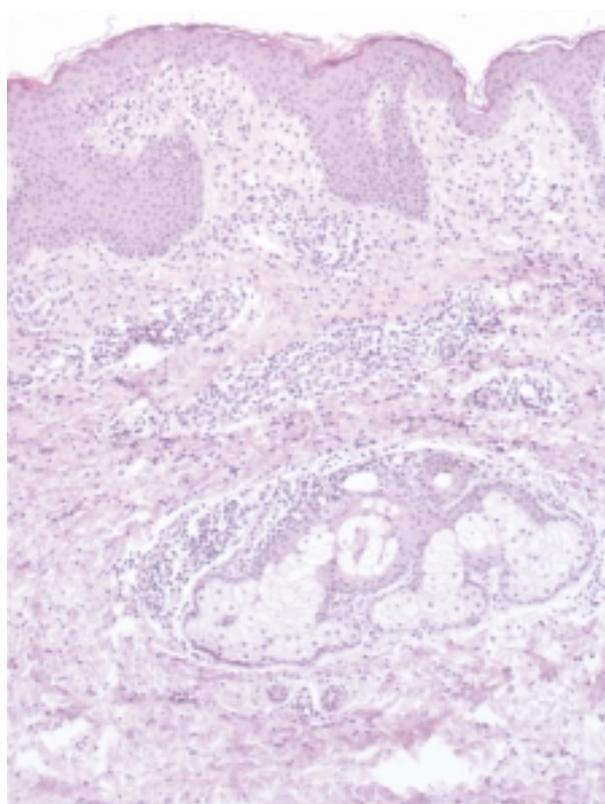


*Figure 1.* Pustular erythematous eruption on the third day of hospitalization.

wheezing. She was hospitalized and blood samples were taken for routine examination, including mononucleosis and rubella–rubeola serology. All medications were stopped and cold compresses were applied for the fever.

A complete blood count revealed hemoglobin 11.8 g, hematocrit 32.6%, white blood cell count 26 600/mm<sup>3</sup> (neutrophils 49%, lymphocytes 39% and monocytes 12%), platelet count 174 000/mm<sup>3</sup>, and erythrocyte sedimentation rate 20 mm in the first hour. Her liver function tests were abnormal: direct bilirubin 1.4 mg/dL, indirect bilirubin 2.0 mg/dL, aspartate aminotransferase 178 U/L, alanine aminotransferase 229 U/L, alkaline phosphatase 118 U/L, serum albumin 3.2 g/dL, and prothrombin time 12 seconds. Viral hepatitis serology (IgM antibody to hepatitis A antigen, hepatitis B surface antigen, and hepatitis C antibody) were negative. Although there was frank hematuria, the levels for urea, creatinine, uric acid, and electrolytes in blood were within normal limits. Rubella–rubeola serology revealed high specific IgG levels and were negative for specific IgM; so these viral infections were ruled out. A mononucleosis spot test was also negative. Levels of complement components C3 and C4 were low (C3, 44.5 mg/dL and C4, 4.0 mg/dL) and autoimmune screens consisting of antinuclear, anti-double-stranded DNA, anti-smooth-muscle, and anti-liver-kidney-microsome antibodies were negative. Abdominal ultrasound showed uniform liver enlargement with a slight increase in echo texture, and there was no evidence of portal hypertension or biliary obstruction. Her chest radiograph was unremarkable and blood cultures were negative.

Microscopic examination of the skin biopsy showed moderate to severe mononuclear inflammatory cell infiltration especially in perivascular, interstitial and periadnexal areas of the dermis (Figure 2). Inflammatory cell populations were rich in lymphocytes and eosinophils. The epithelia of some hair follicles containing inflammatory cells that were mostly neutrophils. Capillary congestion, extravasation of erythrocytes and some melanophages were observed in the dermis. The epidermis revealed focal and irregular acanthosis, mild spongiosis,



*Figure 2.* Inflammatory cell infiltration especially in perivascular and periadnexal areas of the dermis (hematoxylin and eosin stain;  $\times 40$ ).

focal parakeratosis, and focal vacuolar change in the basal layer. Morphologic findings were consistent with a diagnosis of drug eruption, which was evaluated together with clinical history.

A diagnosis of DHS was thus based on the patient's medical history, clinical findings and laboratory test results. She was put on a gluten free diet, and glucocorticoid therapy was started. Corticosteroids were given both orally (prednisolone 40 mg/d) and topically (beclomethasone dipropionate ointment 0.025%, 2 times a day). Cetirizine 10 mg/d and hydroxyzine 25 mg/d were added for pruritus. Her clinical condition improved quickly, and laboratory test results returned to normal levels within 2 weeks. We planned to taper off her corticosteroid therapy over a period of 6 weeks and she was discharged. After 8 weeks, her follow-up examination and laboratory results were normal.

## Discussion

Dapsone (4, 4'-diamino-diphenyl sulfone) is the parent compound of sulfone drugs. Synthesized in 1908, its antibacterial characteristics were not noticed until several decades later. Dapsone has been used as a first-line treatment for leprosy since the 1950s [2]. It is also the drug of choice for the management of dermatitis

herpetiformis. Although good results may be obtained for some patients with a gluten-free diet, the difficulty of dietary adherence makes dapsone the drug of choice for many. Itching and blister formation can be controlled with 100 to 200 mg/d of dapsone in most [1].

Dapsone is absorbed well from the gut and primarily metabolized through N-acetylation and N-hydroxylation (oxidation) [3]. The hydroxylamine metabolite and other hydroxylated metabolites are potent oxidants and have been thought to cause the hematologic adverse effects associated with dapsone, including methemoglobinemia and hemolytic anemia [3]. It is excreted by the kidney, but has significant enterohepatic circulation [4]. Thus, a long elimination half-life (between 24 and 30 hours on the average) is important to remember in case adverse reactions emerge after a long metabolite impact period [4].

Several drugs, including anticonvulsants, sulfonamides, dapsone, allopurinol, and minocycline, may cause a severe hypersensitivity syndrome that consists of fever, rash, lymphadenopathy and different degrees of organ involvement. This entity is also termed drug reaction with eosinophilia and systemic symptoms (DRESS) [5], and DHS has been considered a manifestation of DRESS syndrome. Typically the symptoms begin within several weeks of commencing therapy. Patients present with fever, malaise, a generalized cutaneous eruption, lymphadenopathy, hemolytic anemia, and hepatitis. The rash, which is often initially a benign morbilliform eruption, may develop into frank exfoliative dermatitis [3, 5-7]. Liver involvement displays a mixed hepatocellular and cholestatic pattern [6] although drug-induced cholangitis has been reported in a patient with DHS [8]. According to Richardus and Smith [9], a true diagnosis of DHS should be made based on the following criteria: a) symptoms manifesting within 8 weeks of starting therapy and resolving after withdrawal of the drug, b) symptoms not attributable to any other drug used simultaneously, and c) symptoms unrelated to leprosy or any underlying disease.

It is presumed that hydroxylated metabolites are important in the pathogenesis of DHS. A reduction in N-hydroxylation enzyme levels or activity results in decreased total clearance of dapsone [6]. Aging or preexisting liver disease may offer relative protection against adverse effects because of decreased enzyme activity and, therefore, decreased production of toxic metabolites [6]. The long elimination half-life that averages between 24 and 30 hours is thought to be due to significant enterohepatic recirculation of the drug [3]. Strong protein binding of the drug itself (70%-90%) and its major metabolite, monacetyl dapsone (99%), contribute to that long half-life [4]. Systemic

corticosteroids have been used to treat DHS; however, no comparative studies regarding their effectiveness have been performed to date. Since dapsone persists up to 35 days in organs through protein binding and enterohepatic recirculation, slow tapering off the corticosteroid therapy over at least 1 month with close monitoring of organ function is required.

Generally DHS is a self-limiting drug reaction and most patients recover following cessation of dapsone therapy and application of corticosteroid therapy; however, deaths have been reported [10]. Physicians, especially those dealing with leprosy treatment or working in the fields of dermatology and allergy, should be aware of this infrequent but potentially fatal severe form of adverse reaction that can mimic other conditions.

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Osman Sener

Gulhane Military Medical Academy  
Division of Allergy  
06018 Etlik, Ankara, Turkey  
E-mail: drosmansener@yahoo.com