

Dapsone hypersensitivity syndrome with circulating 190-kDa and 230-kDa autoantibodies

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Summary

Dapsone has potent anti-inflammatory effects, and is used in the treatment of leprosy, cutaneous vasculitis, neutrophilic dermatoses, and dermatitis herpetiformis and other blistering disorders. However, it may cause severe adverse reactions such as hypersensitivity syndrome, which is characterized by fever, skin rash, hepatitis and lymphadenopathy. We report a 44-year-old female Korean patient with dapsone hypersensitivity syndrome (DHS) that presented as a bullous skin eruption. The patient had a 1-year history of urticarial vasculitis, treated with antihistamines, prednisolone and dapsone. Although the skin lesions improved, she reported fever, nausea, abdominal pain, jaundice, fatigue and skin rashes. On physical examination, there were generalized erythematous macules and purpura with facial oedema that developed into vesicles on the upper limbs. Histological examination of a skin biopsy of a vesicular lesion found subepidermal oedema with a mixed inflammatory cell infiltrate, including eosinophils in the dermis. Indirect immunofluorescence testing using normal foreskin as substrate revealed IgG deposits in the basement membrane zone. Circulating autoantibodies against antigens of 190 and 230 kDa were found by immunoblotting analysis using epidermal extracts. This case illustrates DHS with the formation of circulating autoantibodies.

Dapsone (4,4'-diaminodiphenyl sulfone), a potent anti-inflammatory and antiparasitic compound, is used for a variety of dermatological conditions including leprosy, autoimmune bullous diseases, leucocytoclastic disorders and other forms of vasculitis. Dapsone may cause a severe idiosyncratic reaction known as dapsone hypersensitivity syndrome (DHS), which presents with a triad of fever, rash and internal organ involvement.¹ We report a case of DHS in a patient with urticarial vasculitis, who had diffuse generalized erythema over the entire body surface associated with tense vesicles and bullae on the limbs. The immunofluorescence and

immunoblotting studies showed circulating autoantibodies targeting epidermal antigens in the patient.

Report

In December 2004, a 44-year-old Korean woman visited the emergency department with pruritic, erythematous generalized oedematous patches associated with vesicles and bullae on the limbs, which had been present for 3 days. The patient reported fever and tenderness on the right upper abdomen. She had been treated for urticarial vasculitis with 100 mg of dapsone, 10 mg of prednisolone and 10 mg of ebastine, a non-sedating H1 antihistamine. She had been taking the medications for 1 month, and had then developed generalized skin rash with fever. The patient's family history was noncontributory.

On physical examination, generalized oedema with diffuse erythema was seen over the entire body surface, and tense vesiculobullous lesions were present on the

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forearms (Fig. 1). The oral and genital mucosae were intact. Multiple enlarged cervical lymph nodes were palpable. The patient had a persistent fever ($> 38^{\circ}\text{C}$).

Laboratory investigations revealed leucocytosis (white blood cell count $16.2 \times 10^9/\text{L}$; normal range $4\text{--}10 \times 10^9/\text{L}$), abnormal liver function [aspartate aminotransferase 248 U/L (normal range $10\text{--}35$ U/L); alanine transferase (ALT) 196 U/L ($10\text{--}40$ U/L); gamma glutamyl transferase 214 U/L ($5\text{--}41$ U/L); total bilirubin 3.8 mg/dL ($0.22\text{--}1.2$ mg/dL)] and raised lactate dehydrogenase (1741 U/L; normal range $270\text{--}530$ U/L). After admission, the leucocytosis worsened to $22 \times 10^9/\text{L}$, aggravated by atypical lymphocytosis

(10–15%) and eosinophilia (14%; 1–4%). Viral markers for acute hepatitis were negative. Abdominal ultrasonography found parenchymal liver disease.

Histopathological examination of a vesicle from forearm found subepidermal bullae due to marked oedema in the upper dermis and perivascular lymphocytic infiltrates with eosinophils (Fig. 2a). To exclude the possibility of drug-induced autoimmune bullous disease, we performed indirect immunofluorescence (IIF) and immunoblotting analyses of the patient's serum. IIF on normal human foreskin showed deposition of immunoglobulin G linearly along the basement membrane zone (BMZ) (Fig. 2b). Immunoblotting using



Figure 1 (a) Generalized oedematous erythema on the face and (b) erythematous patches with tense vesiculobullae on the forearms.

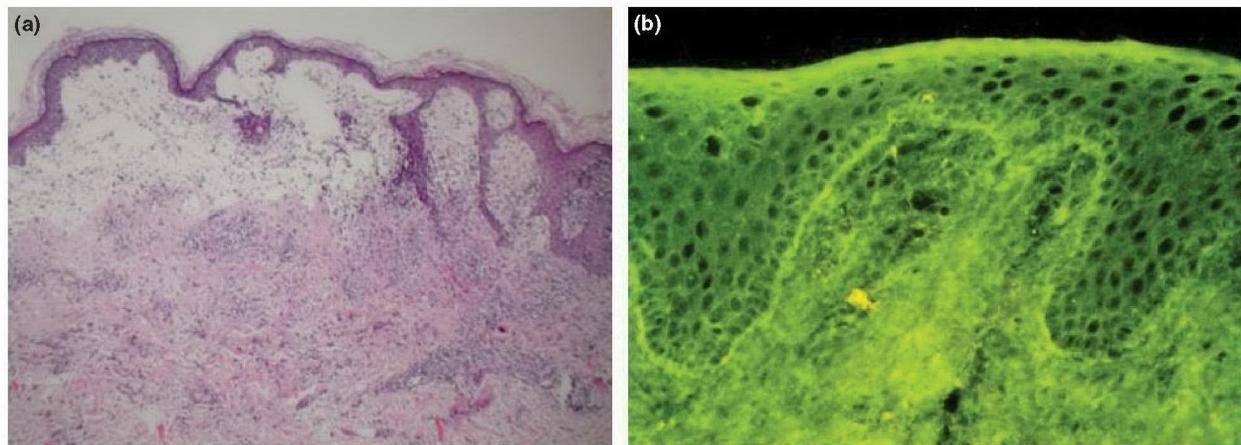


Figure 2 (a) Subepidermal bullae due to marked oedema in the upper dermis, and moderately dense mixed inflammatory cell infiltrates with lymphocytic predominance (haematoxylin and eosin, original magnification $\times 40$). (b) Indirect immunofluorescence revealed linear IgG deposits along the basement membrane zone (original magnification $\times 400$).

human epidermal extracts demonstrated IgG antibodies bound to polypeptides of 190 and 230 kDa (Fig. 3). ELISA using antidesmoglein (Dsg)-1, anti-Dsg-3, anti-bullous pemphigoid (BP)180NC16a and anti-BP230 was performed at 1 : 100 dilution; the results were negative. To exclude viral activation, especially human herpesvirus (HHV)-6 which is implicated in drug-induced hypersensitivity syndrome, we performed HHV-6 gene nested PCR (GenBank accession No. S57540) using the patient's serum, but no PCR product was found.

Dapsone was discontinued and the patient was treated with antihistamines and prednisolone 25 mg/day. Subsequently, the skin rash became dusky exfoliative patches and the laboratory results normalized without fever. The patient was diagnosed with DHS.

DHS is a severe idiosyncratic drug reaction characterized by the clinical triad of fever, rash and systemic involvement. Various types of rashes develop in DHS, such as maculopapular/pustular/vesiculobullous eruption, exfoliative dermatitis, erythroderma and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). The pathophysiology of DHS remains unclear,

but it may be caused by dapsone metabolites forming haptens, resulting in the formation of antidapsone antibodies.¹

Because our patient with DHS had multiple vesiculobullous lesions, we tested for autoimmune bullous diseases using histopathology, IIF test, immunoblotting, and ELISA. We found deposition of IgG antibodies along the BMZ using IIF. The immunoblotting assay revealed that the autoantibodies from the patient's serum were bound to antigens of 190 and 230 kDa in size, which were compatible with the molecular weight of periplakin and BP230, respectively. The ELISA did not detect antibodies against 230-kDa antigens. Our findings suggest a difference in the sensitivity of the ELISA compared to the immunoblotting assay, which resulted in inconsistent data. In assessing the index value for ELISA, the final absorbance obtained might not necessarily represent an accurate estimate of the concentration of the autoantibodies.² Another consideration is that the target antigens that caused antibody production in this patient may be heterogeneous. In addition, the autoantibodies found by IIF and immunoblotting might not have been specific for periplakin or BP230, even though the molecular weight of the autoantibodies were similar. Moreover, there are several studies about the association of drug-induced bullous dermatosis with positive IF findings and negative IIF and ELISA, with no clear explanation for these results.^{3,4} These results suggest that circulating autoantibodies might be produced after dapsone exposure, which trigger DHS. Formation of autoantibodies to the 190-kDa and 230-kDa antigens in our patient with DHS was unrelated to autoimmune bullous disease, a finding that is of particular interest. There are reports of autoantibody formation associated with administration of carbamazepine.^{5,6} The exact role of the autoantibodies found in drug-induced hypersensitivity syndrome remains unknown. Dapsone is metabolized primarily via *N*-acetylation and *N*-hydroxylation (oxidation). The *N*-hydroxylation pathway is thought to be the initial step in the formation of toxic intermediate metabolites, including hydroxylamine.¹ These metabolites covalently bind to or modify various molecules, including major histocompatibility complex peptides, so that drug-specific T-cell recognition contributes to DHS. Reactive metabolites act as haptens and bind to endogenous proteins to form a compound that triggers an immune reaction. Haptenated compounds may also be directly toxic to cells.⁷ Thus, the autoantibodies detected in our case might be a secondary phenomenon during the immune reaction, not the primary pathogenic event.

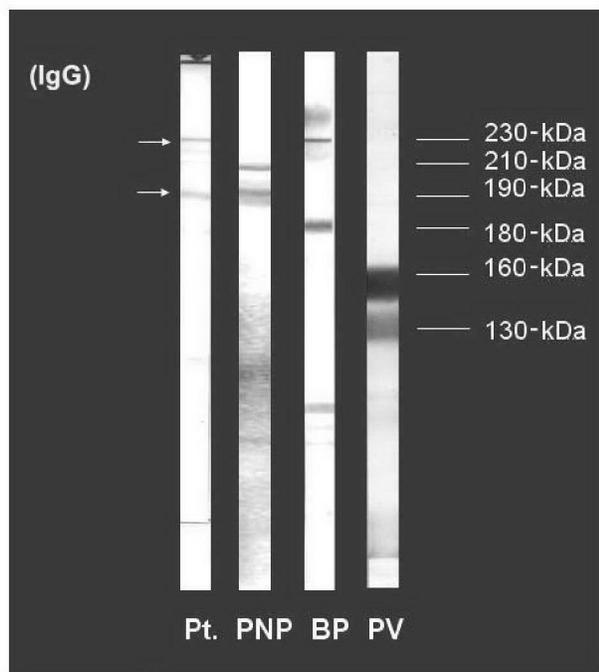


Figure 3 Immunoblotting assay using human foreskin epidermal extracts. Lane 1, patient's serum; lane 2, paraneoplastic pemphigus serum with autoantibodies to 190-kDa and 210-kDa antigens; lane 3, bullous pemphigoid serum with autoantibodies to 180-kDa and 230-kDa antigens; lane 4, pemphigus vulgaris serum with autoantibodies to 160-kDa and 130-kDa antigens.

Recent studies have shown that HHV-6 and HHV-7 might also be involved in drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, although the precise role and preceding order in the pathogenesis remains unclear.⁸ However, we found no evidence of HHV-6 activation in our patient with DHS. The pathogenesis of DHS is likely to involve complex immune interactions.

Whether we consider our case as DHS or bullous drug eruption is another controversial question. DHS is regarded as a form of DRESS syndrome induced by dapsone. The current definition of DRESS does not characterize and describe the nature of rash, but some authors suggest that all drug eruptions should be classified according to the cutaneous lesions of the most pronounced pathology.^{9,10} SJS/TEN are also regarded as DRESS with severe skin reaction, but they show different characteristics, treatment and prognosis compared with DRESS. There are still arguments for and against the current definition and classification of DRESS.

In conclusion, the detection of circulating autoantibodies might provide another clue towards understanding the pathogenesis of DHS.

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