

A case of drug-induced hypersensitivity syndrome due to diaminodiphenyl sulfone complicated by acute respiratory failure with atypical erythema around existing prurigo

Dear Editor,

Drug-induced hypersensitivity syndrome (DIHS) is a complex condition caused by drug allergy and virus reactivation. The annual prevalence of DIHS is 0.9 per 100 000 persons, and mortality rates have been reported to range from 5% to 10%.¹ Eosinophil elevation is seen in 95% of cases.² We report a case of DIHS due to diaminodiphenyl sulfone (dapson) complicated by acute respiratory failure. Intriguingly, the blood eosinophil count was normal, and erythema expanded from prurigo. Overall steroid reactivity was favorable.

A 79-year-old man had been receiving treatment for refractory nodular prurigo for 5 years. He started taking dapson for possible pemphigoid nodularis 5 weeks before hospitalization (Figure 1A,B). After 3 weeks, the patient experienced general malaise and dyspnea with erythema exsudativum around the prurigo eruptions (Figure 1C,D). The patient's white blood cell count was elevated, including atypical lymphocytes, without elevated eosinophil count. In addition to both hepatic impairment and renal impairment, the patient developed type I respiratory failure. Chest CT showed diffuse reticular shadows with bilateral pleural effusion and mediastinal lymphadenopathy (Figure 1E,F). Skin biopsy revealed vacuolar degeneration of the basal cells and infiltration of lymphocytes around blood vessels of the upper dermis without epidermal necrosis (Figure 1G). Moreover, the IgG titer against human herpesvirus 6 increased from $\times 40$ (1 week after onset) to $\times 1260$ (3 weeks after onset). The drug lymphocyte stimulation test of dapson was positive (328%). Based on these findings, we diagnosed this case as DIHS caused by dapson. Immediately after discontinuing dapson, high-dose methylprednisolone pulse therapy was administered. Oral prednisolone 40 mg per day was administered and tapered to 0 mg by 15 weeks. A marked improvement was observed in the respiratory function and skin manifestations (Figure 1H,I).

There are four reports in the literature of DIHS cases induced by dapson complicated by respiratory dysfunction.^{3,4} Eosinophil elevation was observed in 75% of these cases. In order to find disease marker for which cases show respiratory symptoms due to DIHS, future case accumulation is necessary, while all patients improved with gradual steroid tapering. We consider that steroid responsiveness

may be relatively favorable in cases of dapson-induced DIHS comorbid with acute respiratory failure.

The balance of effector T cells and regulatory T cells (Tregs) has been reported to play a role in the pathogenesis of DIHS. Increased expression of Tregs at onset leads to the suppression of effector T cells and reactivation of human herpesvirus 6, resulting in delayed onset, bimodal rash, and prolonged symptoms.⁵ The proportion of Tregs in DIHS cases tends to be higher than those in toxic epidermal necrolysis cases, although the difference is not significant (Figure 1J). In the present case, the proportion of Tregs was higher after onset compared with before onset (Figure 1K). However, the proportion was the lowest among other DIHS cases (Figure 1J). This finding may be related to the acute exacerbation and favorable steroid responsiveness.

We report a case of DIHS induced by dapson with comorbid respiratory dysfunction and atypical erythema around existing prurigo. The causative drug and the low proportion of Tregs in the skin may predict the response to steroid treatment in DIHS.


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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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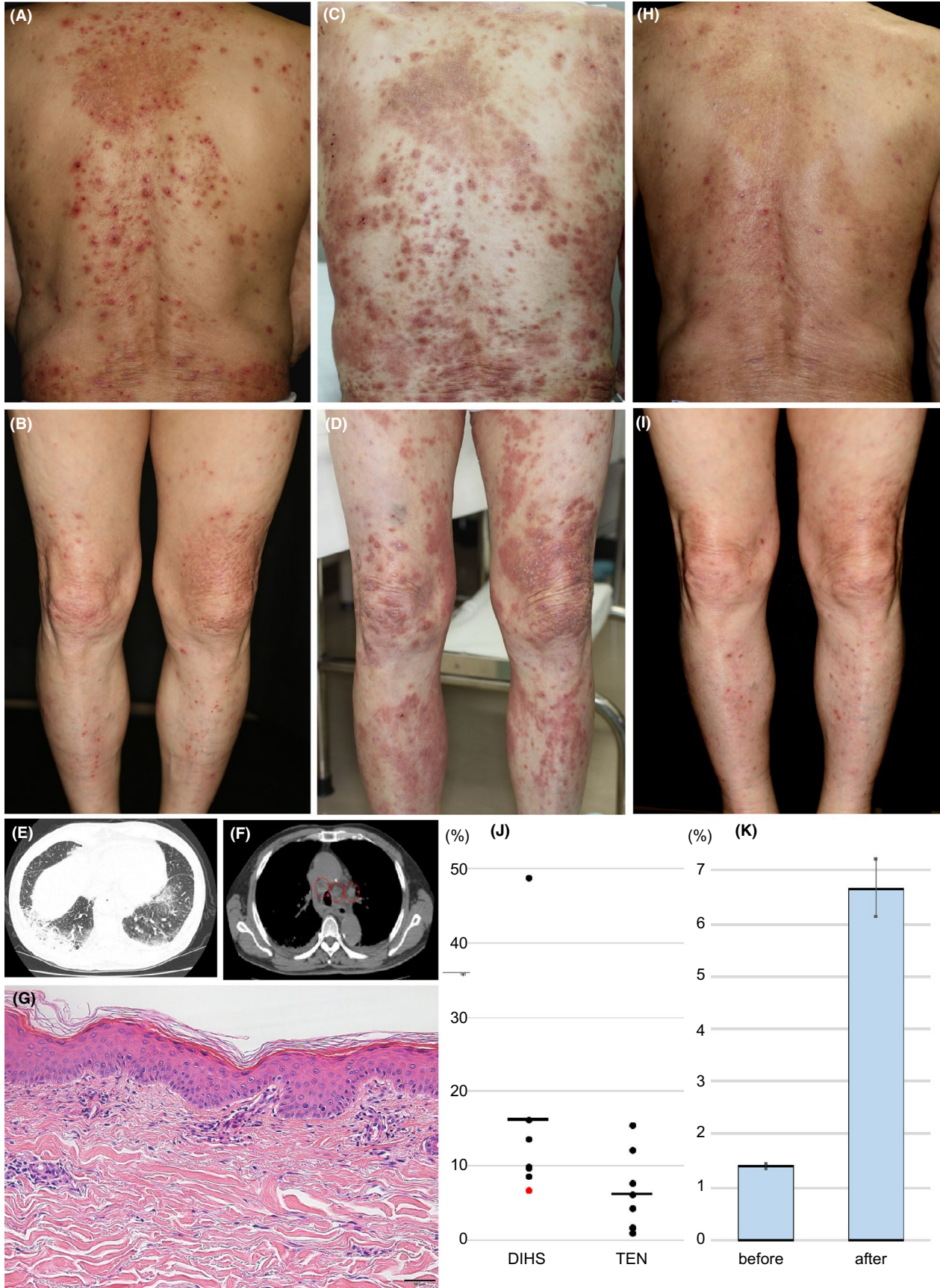


FIGURE 1 Analysis of symptoms and regulatory T-cell ratio in the skin from the patient with drug-induced hypersensitivity syndrome (DIHS) by diaminodiphenyl sulfone with acute respiratory failure. A, B, Prurigo before the onset of drug-induced hypersensitivity syndrome (DIHS). C, D, Erythema spreading around the preexisting prurigo at the onset of DIHS. H, I, After DIHS treatment. E, F, Chest CT at the onset of respiratory failure. E, Diffuse reticular shadow with bilateral pleural effusion in the pulmonary windows. F, Mediastinal lymphadenopathy in the mediastinal window. Blood pressure was 95/57, SpO₂ was 90% (sitting position): 84% (decubitus position), and body temperature was 37.8°C. G, Histopathological image of the affected skin lesion at the onset of DIHS. Vacuolar degeneration of the basement membrane and infiltration of lymphocytes around blood vessels; scale bar = 50 μm. J, The proportion of Tregs in T cells was calculated by counting the number of FOXP3-positive cells within CD3-positive cells. Two independent visual fields at 200× magnification for each section were counted by two independent investigators. Paraffin-embedded skin sections derived from 6 DIHS patients and 7 toxic epidermal necrolysis (TEN) patients in Osaka University were used. The present case is indicated by a red circle. The proportion of Tregs/T cells tended to be elevated in the sections of DIHS cases compared with those of the TEN cases, although this difference was not significant. The proportion of Tregs/T cells in the section of the present case is the lowest counted within the sections of DIHS patients. K, The proportion of Tregs in T cells in the present case before and after onset.

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REFERENCES

1. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. *Am J Med.* 2011;124(7):588–97.
2. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol.* 2013;169(5):1071–80.
3. Jaffuel D, Lebel B, Hillaire-Buys D, Pene J, Godard P, Michel FB, et al. Eosinophilic pneumonia induced by dapsone. *BMJ.* 1998;317:181.
4. Janier M, Guillevin L, Badillet G. Pulmonary eosinophilia associated with dapsone. *Lancet.* 1994;343:860–1.
5. Takahashi R, Kano Y, Yamazaki Y, Kimishima M, Mizukawa Y, Shiohara T. Defective regulatory T cells in patients with severe drug eruptions: timing of the dysfunction is associated with the pathological phenotype and outcome. *J Immunol.* 2009;182:8071–9.

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