

## Drug-induced Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms Caused by Lenalidomide: Case Report and Review of the Literature

Shin-Ichi OSADA<sup>1,2</sup> and Takahiko SATO<sup>1</sup>

<sup>1</sup>Department of Dermatology and Plastic Surgery, Akita University Graduate School of Medicine, Akita and <sup>2</sup>Department of Dermatology, Nippon Medical School Tama Nagayama Hospital, 1-7-1 Nagayama, Tama City, 206-8512 Tokyo, Japan. E-mail: osada0130@nms.ac.jp  
Accepted May 19, 2021; Epub ahead of print May 24, 2021

Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, adverse drug reaction with acute skin rash, fever, lymphadenopathy, eosinophilia, and the involvement of at least one internal organ (especially the liver) (1, 2). Drug allergy and viral reactivation are implicated in the pathogenesis of this disease; DiHS and DRESS could be part of the continuum of the same disease (1), although human herpes virus-6 (HHV-6) reactivation is not included in the DRESS criteria (3). Epstein-Barr virus (EBV), cytomegalovirus (CMV), and HHV-6 are also reactivated during the course of DiHS/DRESS (1). We report here the first case of DiHS/DRESS caused by lenalidomide, a derivative of thalidomide with more potent immunomodulatory and anti-tumor activities, in which both HHV-6 and CMV were reactivated.

### CASE REPORT

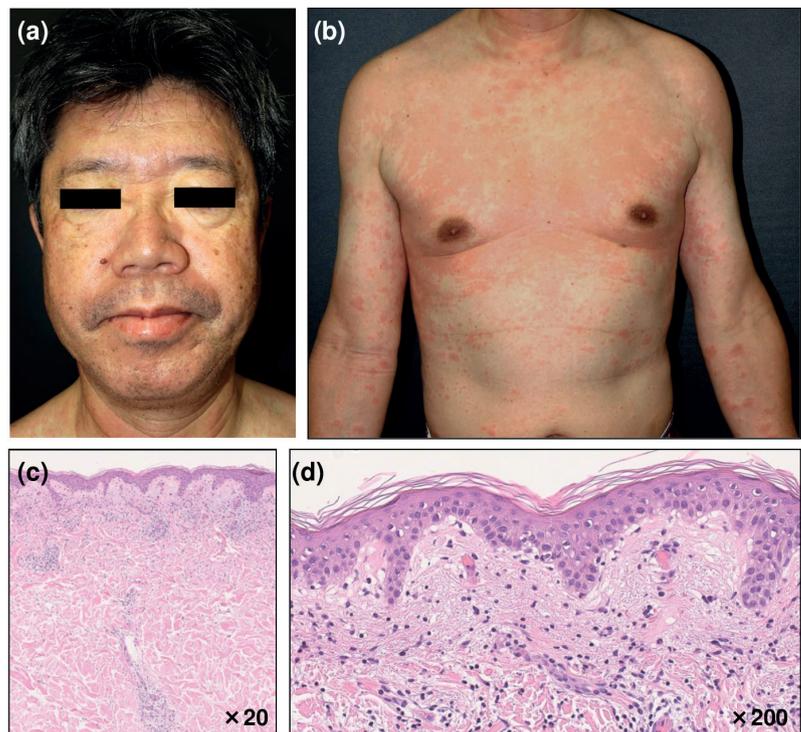
A 59-year-old man presented with a maculopapular pruritic rash on the face, trunk, upper and lower extremities associated with fever ( $>38.5^{\circ}\text{C}$ ), periorbital oedema, swelling of the lower lip, and mild cervical lymphadenopathy (Fig. 1a, b). He was treated for multiple myeloma and received a combination therapy with bortezomib, lenalidomide, and dexamethasone (VRd). Despite the patient developing a rash 9 days after completing the first cycles of VRd therapy, the second cycle was continued and completed. Laboratory tests revealed leukocytosis (11,900 cells/l; normal value  $<9,000$  cells/l), eosinophilia (2,980 cells/ $\mu\text{l}$ ; normal  $<500$ / $\mu\text{l}$ ), monocytosis (1,190 cells/ $\mu\text{l}$ ; normal 90–690/ $\mu\text{l}$ ) and atypical lymphocytes (2%). Increased serum alanine aminotransferase (61 U/l; normal 5–40 U/l), lactate dehydrogenase (342 U/l; normal 115–245 U/l), and  $\gamma$ -glutamyl transpeptidase (89 U/l; normal  $<70$  U/l), and decreased serum IgG (510 mg/dl; normal 861–1,747 mg/dl), IgM (7 mg/dl; normal 33–183 mg/dl), and IgA (15 mg/dl; normal 93–393 mg/dl) levels were also observed. Viral reactivation was detected; titres of anti-human herpes virus-6 (HHV-6) IgG (using immunofluorescence assay) and anti-cytomegalovirus (CMV) IgG (using enzyme immunoassay) increased from  $<10$  fold (at presentation) to  $\times 640$  fold (on day 40) and from 9.3 IU/ml (at presentation) to 17.9 IU/ml (on day 40), respectively.

A biopsy was taken from an infiltrated erythema on the patient's abdomen, and showed perivascular lymphocytic infiltration in the upper dermis and liquefaction degeneration at the dermoepidermal

junction (Fig. 1c, d). These clinical and laboratory data fulfilled the diagnostic criteria for DiHS/DRESS (Table I) (1, 2). Monocytosis and a marked decrease in serum Ig levels confirmed an acute phase of DiHS/DRESS (1). The patient's cutaneous manifestations and pruritus persisted after the discontinuation of lenalidomide. Administration of prednisolone (20 mg/day) improved these symptoms; it was gradually tapered and ceased in 3 weeks, without recurrence. Since thalidomide and its derivatives is critical to prevent the growth of myeloma cells, pomalidomide, another thalidomide derivative, was administered to the patient. The cutaneous pruritic manifestations reappeared after administering pomalidomide. These results indicated that thalidomide derivatives were causative agents for DiHS/DRESS in this patient. Eventually, the patient achieved complete remission with an autologous haematopoietic stem cell transplant. DiHS/DRESS is known to be caused by a limited number of drugs, and thalidomide and its derivatives represent potentially responsible drugs for this condition.

### DISCUSSION

There are 4 previous reports on DRESS caused by lenalidomide (Table I) (4–7). Since HHV-6 reactivation is



**Fig. 1.** Clinical presentations of (a) the face and (b) the trunk at the first visit. Histopathology of a biopsy specimen. Perivascular lymphocytic infiltration in the upper dermis (c) and liquefaction degeneration at the dermoepidermal junction (d) (Haematoxylin-eosin staining; original magnifications (c:  $\times 20$ , d:  $\times 200$ )). Permission is given by the patient to publish these photos.

**Table I. Summary of lenalidomide-induced drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) cases**

Primary disease	Age, years/Sex	Medical history	Time interval <sup>a</sup>	HHV-6 reactivation	DiHS criteria	DRESS criteria (score)	Treatment	Reference
Multiple myeloma	78/F	Hypertension, diabetes mellitus	4 weeks	Positive	Typical 7/7	Definite (7)	PSL 20 mg/day	(4)
Multiple myeloma	65/F	Acute interstitial nephritis	4 weeks	Negative	Atypical 5/7	Definite (7)	PSL 80 mg/day	(5)
Multiple myeloma	62/F	Chronic kidney disease	5 days	N.D.	Atypical 5/7	Probable (5)	PSL	(6)
Multiple myeloma	75/F	Hypertension, diabetes mellitus	4 weeks	N.D.	Atypical 6/7	Definite (7)	mPSL 80 mg/day	(7)
Multiple myeloma	59/M	Hypertension, Hyperuricemia	5 weeks	Positive	Typical 7/7	Definite (7)	PSL 20 mg/day	Current case

<sup>a</sup>The period before the onset of rash after lenalidomide administration.

HHV-6: human herpes virus-6; mPSL: methylprednisolone; N.D.: no description; PSL: prednisolone.

not included in the DRESS criteria (2), HHV-6 reactivation was investigated in only 2 cases (excluding the current case) and found in one. Since the current case fulfilled both the DiHS and DRESS criteria, this case is the second definite DRESS with HHV-6 reactivation or typical DiHS. CMV reactivation was also detected in the current patient. A recent report has clarified that CMV DNA positivity affects the clinical course and prognosis of patients with DiHS/DRESS; CMV DNA-positive cases took a more severe and protracted course and had a higher risk of developing CMV-related complications, such as pneumonia, peritonitis, and intestinal bleeding (8). Since CMV reactivation was not investigated in other cases, its involvement in the pathogenesis of lenalidomide-DiHS/DRESS cases have to be confirmed by further studies.

As shown in Table I, all patients with DiHS/DRESS caused by lenalidomide had a medical history of hypertension, diabetes mellitus, and/or renal dysfunction, suggesting that these underlying conditions could be risk factors for lenalidomide-related-DiHS/DRESS. Alternatively, the drugs used for treating these diseases may affect the immunomodulatory activity of lenalidomide.

What is the mechanism for lenalidomide caused DiHS/DRESS? Reductions in CD56<sup>+</sup> NK cells, CD19<sup>+</sup> B cells and serum Ig levels and increases in CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> Tregs are observed in the acute phase of DiHS/DRESS (1). Thalidomide, lenalidomide, and pomalidomide bind to cereblon (CRBN), which activates the enzymatic activity of the CRBN E3 ubiquitin ligase complex, leading to the ubiquitination and proteasome-dependent degradation of Ikaros and Aiolos (transcription regulators of B cell development) (9, 10). Under normal conditions, Ikaros stimulates the expression of interferon regulatory factor 4 (IRF4), a key regulator of B cell development at the pre-B cell stage and plasma cell differentiation. Aiolos is required for normal plasma cell development in mice. Thus, the degradation of Ikaros and Aiolos by lenalidomide suppresses the function of B cells and myeloma growth.

Lenalidomide also affects T cell function through IL-2, which is required for the maintenance of Tregs (11). Since Ikaros normally suppresses IL-2 expression in T cells, its loss due to lenalidomide may activate T-cell mediated immune responses and increase the Treg population by the upregulation of IL-2 production.

Causative agents of DiHS/DRESS, such as anticonvulsants and sulphonamides, commonly affect B cell

differentiation and inhibit immunoglobulin production, although they have different pharmacological effects. However, the molecular mechanism underlying the immunosuppressive effects of these drugs remains to be elucidated. Although the number of DiHS/DRESS cases caused by thalidomide derivatives is still limited, analysis of the cereblon-Ikaros/Aiolos-IRF4/IL-2 signalling pathway could be helpful in clarifying the mechanism of the impairment of B and T cell functions in DiHS/DRESS.

*The authors have no conflicts of interest to declare.*

## REFERENCES

- Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): an update in 2019. *Allergol Int* 2019; 68: 301–308.
- Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. *Clin Exp Dermatol* 2011; 36: 6–11.
- 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: 1071–1080.
- Foti C, Antelmi A, Mazzocca A, Saverio Vella F, Romita P, Pugliese S, et al. Drug reaction with eosinophilia and systemic symptoms caused by lenalidomide. *Eur J Dermatol* 2012; 22: 799–800.
- Shaaban H, Layne T, Guron G. A case of DRESS (drug reaction with eosinophilia and systemic symptoms) with acute interstitial nephritis secondary to lenalidomide. *J Oncol Pharm Pract* 2014; 20: 302–304.
- Vlachopoulos G, Kokkona A, Zerva A, Stavroulaki E, Zachariouannis C, Agrafiotis A. Atypical DRESS syndrome induced by lenalidomide in chronic hemodialysis. *J Clin Exp Pathol* 2016; 6: 277.
- Shanbhag A, Pritchard ER, Chatterjee K, Hammond DA. Highly probable drug reaction with eosinophilia and systemic symptoms syndrome associated with lenalidomide. *Hosp Pharm* 2017; 52: 408–411.
- Mizukawa Y, Hirahara K, Kano Y, Shiohara T. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms severity score: a useful tool for assessing disease severity and predicting fatal cytomegalovirus disease. *J Am Acad Dermatol* 2019; 80: 670–678.e2.
- Krönke J, Udeshi ND, Narla A, Grauman P, Hurst SN, Mcconkey M, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. *Science* 2014; 343: 301–305.
- Lu G, Middleton RE, Sun H, Naniong MV, Ott CJ, Mitsiades CS, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science* 2014; 343: 305–309.
- Fontenot JD, Rasmussen JP, Gavin MA, Rudensky AY. A function for interleukin 2 in Foxp3-expressing regulatory T cells. *Nat Immunol* 2005; 6: 1142–1151.