

## Treatment of drug-induced hypersensitivity syndrome with cyclosporine

Sir,

Drug-induced hypersensitivity syndrome, also known as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, is a rare, severe cutaneous adverse reaction characterized by fever, rash, lymphadenopathy, eosinophilia and/or other leukocyte abnormalities, and internal organ involvement. With an estimated mortality rate of 10–20%, timely treatment of drug hypersensitivity syndrome is important.<sup>1</sup> Treatment involves

discontinuation of suspected causative medication, supportive care, and systemic corticosteroids. Here, we present a patient with drug hypersensitivity syndrome, who showed suboptimal response to oral corticosteroids and was subsequently treated successfully with a short course of cyclosporine therapy.

A 48-year-old man weighing 60 kg was transferred from a local community hospital history of intermittent fever and rash od one



**Figure 1:** Erythematous edematous papules on the forearms; erythema and swelling of the face



**Figure 2:** Exfoliative dermatitis over the front of the body

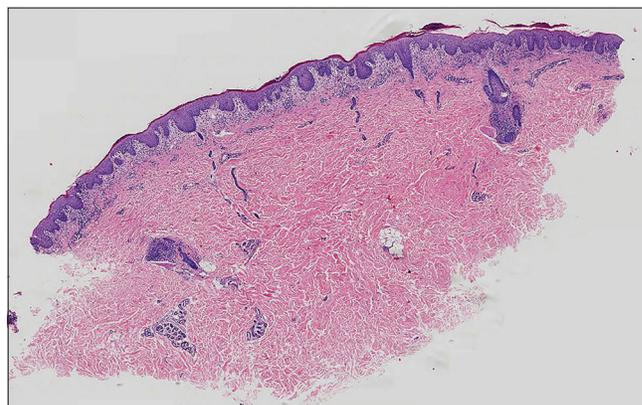
**Table 1: Laboratory data of the patient**

Laboratory Features	Normal value	Days after skin eruption					
		6 days	9 days	16 days	30 days*	37 days†	51 days
WBC	4.0-10.0×10 <sup>3</sup> /mm <sup>3</sup>	13.44	19.26	21.75	11.86	10.22	12.28
Eosinophils (%)	0.5-5.0%	5.9	12.6	15.9	29.5	4.7	8.2
Eosinophil counts	0.02-0.5×10 <sup>3</sup> /mm <sup>3</sup>	0.79	2.42	3.46	3.5	0.48	1.01
TBIL	5-21 μmol/L	13.9	13	23.8	19.9	13.8	26.3
ALT	<42 U/L	70	84	123	97	50	13
AST	<37 U/L	53	32	27	46	35	18
LDH	114-240 U/L	301	533	572		277	253
GGT	<50 U/L	161	144	144	40	46	25
SCr	0.51-0.96 mg/dL	0.92	0.70	0.58	0.82	0.53	0.59
BUN	4.86-23.71 mg/dL	18.49	19.54	18.71	19.31	16.54	12.00
Serum potassium	3.5-5.5 mEq/L	3.5	3.0	3.8	5.0	4.6	4.0

\*Laboratory data before cyclosporine therapy; †Laboratory data after 7-day course of cyclosporine. To convert SCr to μmol/L, multiply by 88.4; BUN to mmol/L, multiply by 0.35. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, GGT: Gamma-glutamyl transferase, LDH: Lactate dehydrogenase, SCr: Serum creatinine, TBIL: Total bilirubin, WBC: White blood cells



**Figure 3:** Exfoliative dermatitis over the back of the body

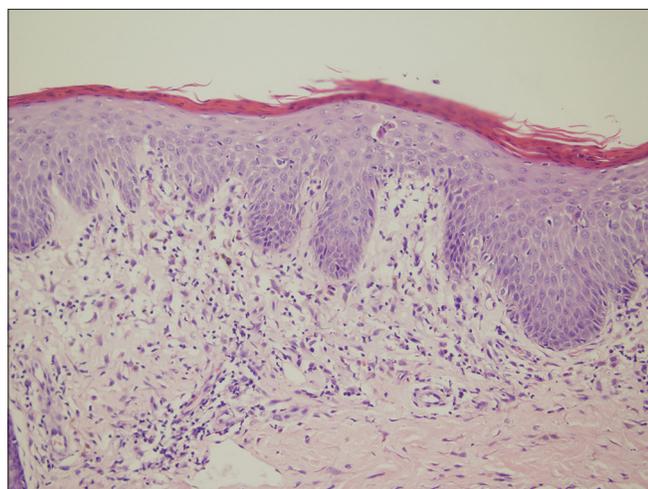


**Figure 4:** Histologic examination shows hyperkeratosis with parakeratosis along with spongiotic dermatitis (H and E, ×20)

month duration. He had a history of ventricular tachycardia and was prescribed mexiletine 2 months ago. Twenty-four days after the initiation of mexiletine, he developed erythematous edematous papules on the forearms and significant erythema and swelling of

the face [Figure 1]. Erythematous edematous papules gradually progressed to involve the chest, back, and proximal extremities. The patient stopped taking mexiletine and was then prescribed prednisolone 100 mg daily for 9 days, which was then tapered to 70 mg daily for 6 days in the community hospital. He rapidly improved, but he weaned himself off prednisolone on his own volition after discharge. He deteriorated within 11 days after the discontinuation of prednisolone and had a widespread exfoliative dermatitis [Figures 2 and 3]. Subsequently, the patient was admitted to our hospital. Clinical examination did not reveal any mucosal involvement. Lymph nodes in the axillary area were palpable. The patient was febrile with a temperature varying between 37.7°C and 39.5°C. Blood pressure was in the normal range (118/72 mmHg), and pulse rate was 104 beats/min. Laboratory examination revealed hypereosinophilia ( $3.5 \times 10^3/\text{mm}^3$ ) and elevated alanine aminotransferase and lactate dehydrogenase levels (alanine aminotransferase, 97 U/L; lactate dehydrogenase, 505 U/L). Renal function test (serum creatinine, 0.82 mg/dL; blood urea nitrogen, 19.31 mg/dL; serum potassium 5.0 mEq/L) was in the normal range [Table 1]. The patient denied infectious symptoms, history of psoriasis, or use of other medication before the onset of the rash. A skin biopsy specimen from the right abdomen revealed parakeratosis along with spongiotic dermatitis, lymphocytes, and mild eosinophil infiltration in the upper dermis, which was consistent

with a drug hypersensitivity reaction [Figures 4 and 5]. Periodic acid-Schiff (PAS) stain was negative for fungi. Based on the clinical findings, the patient was diagnosed as drug-induced hypersensitivity syndrome, which was confirmed using the RegiSCAR criteria for DRESS and drug-induced hypersensitivity syndrome [Table 2].<sup>2</sup> The diagnosis of drug-induced hypersensitivity syndrome was clear,



**Figure 5:** Histologic examination shows spongiotic dermatitis, lymphocytes infiltration in the upper dermis (H and E, ×200)

so HHV-6 serology was not done in our hospital. Using the Naranjo adverse drug reaction probability scale, we determined that the probability of mexiletine causing the drug-induced hypersensitivity syndrome was probable (score of 5).<sup>3</sup>

High blood glucose level of 361.8 mg/dL and strong positive acetone in the urine pointed towards diabetic ketoacidosis, when he was admitted in our hospital. He denied prior history of diabetes mellitus, and blood glucose level was in the normal range during hospitalization in the local community hospital. Diabetic ketoacidosis of the patient was successfully treated by continuous venous drop insulin infusion and fluid replacement. We speculated that diabetes mellitus was the adverse event of corticosteroids. Because systemic corticosteroid therapy was contraindicated, we decided not to use corticosteroids. The patient began a 7-day course of oral cyclosporine at a dose of 5 mg/kg per day divided into twice-daily dosing (150 mg twice daily). Three days after starting treatment with cyclosporine, his eruption started to resolve. After the 7-day course of cyclosporine, his eruption had completely resolved [Figures 6 and 7], and hematological investigation revealed normal alanine aminotransferase concentrations and eosinophil counts (alanine aminotransferase, 50 U/L; eosinophil counts,  $0.48 \times 10^3/\text{mm}^3$ ) [Table 1] (37 days after the onset of the skin eruption). Then, the cyclosporine dosage was tapered gradually to 100 mg twice daily for 14 days and 150 mg daily for 20 days. The patient weaned himself off cyclosporine on his own volition

**Table 2: RegiSCAR criteria for drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome and patient data**

Score	RegiSCAR criteria				Minimum	Maximum	Our patient
	-1	0	1	2			
Fever $\geq 38.5^\circ\text{C}$	No/U	Yes			-1	0	0
Enlarged lymph nodes		No/U	Yes		0	1	1
Eosinophilia		No/U			0	2	
Eosinophils			$0.7-1.499 \times 10^9/\text{L}$	$\geq 1.5 \times 10^9/\text{L}$			2
Eosinophils if leucocytes $< 4.0 \times 10^9/\text{L}$			10%-19.9%	$\geq 20\%$			
Atypical lymphocytes		No/U	Yes		0	1	0
Skin involvement					-2	2	
Skin rash extent (% BSA)		No/U	$> 50\%$				1
Skin rash suggesting DRESS	No	U	Yes				
Biopsy suggesting DRESS	No	Yes/U					
Organ involvement <sup>a</sup>					0	2	
Liver		No/U	Yes				1
Kidney		No/U	Yes				
Muscle/heart		No/U	Yes				
Pancreas		No/U	Yes				
Other organ		No/U	Yes				
Resolution $\geq 15$ days	No/U	Yes			-1	0	0
Evaluation of other potential causes							
Antinuclear antibody							
Blood culture							
Serology for HAV/HBV/HCV							
Chlamydia/mycoplasma							
If none positive and $\geq 3$ of above negative			Yes		0	1	1
Total score					-4	9	6

<sup>a</sup>After exclusion of other explanations. 1: One organ, 2: Two or more organs. Final score:  $< 2$ : No case, 2-3: Possible case, 4-5: Probable case,  $> 5$ : Definite case. DRESS: Drug reaction with eosinophilia and systemic symptoms, U: Unknown/unclassifiable, HAV: Hepatitis A virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, BSA: Body surface area



**Figure 6:** Skin lesions on the front of the body resolved completely after the 7-day course of cyclosporine



**Figure 7:** Skin lesions on the back of the body resolved completely after the 7-day course of cyclosporine

and his skin remained quiescent. The total duration of cyclosporine treatment was 41 days. The renal function, blood pressure, and serum lipids remained within the normal range during cyclosporine treatment [Table 1]. He had no further recurrence of symptoms after 6 months' follow-up.

We found only 4 cases of this condition, successfully treated with cyclosporine reported in the English literature.<sup>4,6</sup> Harman *et al.* reported a patient who developed a reaction to phenytoin and was initially treated with a long tapering course of prednisone. However, after 9 months, she had a recurrence of symptoms. With the patient developing adverse effects of corticosteroids, 4 mg/kg of cyclosporine daily was commenced as a steroid-sparing agent and her skin lesions resolved finally after treatment for 6 months.<sup>4</sup> T-cell production of interleukin-5, leading to eosinophilia may be an important mechanism in the pathogenesis of drug hypersensitivity syndrome. Both corticosteroids and cyclosporine suppress the production of interleukin-5 by T cells. Hence, cyclosporine provides a possible alternative to corticosteroids in the management of drug hypersensitivity. Zuliani *et al.* reported a patient with drug hypersensitivity syndrome induced by vancomycin, with acute interstitial nephritis and hepatitis, who was initially treated with corticosteroids for 3 weeks without any improvement. After tapering the steroids, hemodialysis and 5-day course of cyclosporine was followed by quick resolution of the skin rash and recovery of renal function.<sup>5</sup> Kirhhof *et al.* reported two cases who were treated with 3–7 day course of cyclosporine, resulting in rapid and significant clinical improvement.<sup>6</sup> Lee *et al.* and Daoulah *et al.* also reported patients who were initially treated with corticosteroids but whose conditions continued to worsen. Despite subsequent treatment

with cyclosporine and other immunosuppressive medications, their clinical conditions did not result in clinical resolution.<sup>7,8</sup>

The first case of mexiletine-induced hypersensitivity syndrome was reported by Higa *et al.* in 1997.<sup>9</sup> Although mexiletine is prescribed worldwide, most of the previously reported cases of mexiletine-induced hypersensitivity syndrome have been from Japan, suggesting a genetic predisposition.<sup>10</sup> Despite ethnic differences, the Chinese and Japanese populations share much the same genetic background. The pathogenesis of hypersensitivity is unclear, but probably involves a combination of impaired pharmacokinetics and accumulation of drug metabolites, the sequential reactivation of the herpesvirus family and genetic susceptibility conferred by the association with certain human leukocyte antigen (HLA) class I alleles.<sup>6</sup> The immune system is believed to play a central role in the pathogenesis of drug hypersensitivity syndrome. It is well established that certain human leukocyte antigen haplotypes predispose patients to drug hypersensitivity syndrome. These molecules interact with drug metabolites and are ultimately presented to T cells, resulting in T-cell activation. Recent studies also found a close relationship between human herpes virus 6 (HHV-6) and the development of drug hypersensitivity syndrome. It is hypothesized that T-cell activation may stimulate reactivation and replication of dormant herpesviruses within immune cells. Because cyclosporine targets T cells specifically, by downregulating activation of nuclear factor of activated T cells, it might be an appropriate medication to use in the treatment of this condition.<sup>11</sup>

Systemic corticosteroids are the most widely used systemic therapy for drug hypersensitivity syndrome. However, the adverse effects of long-term systemic corticosteroids can be severe.<sup>6</sup> The rapid and

successful response in our patient suggests that cyclosporine might be a potential alternative to the traditional long course of systemic corticosteroids in the treatment of drug-induced hypersensitivity syndrome, especially if systemic corticosteroid therapy is contraindicated.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

#### Financial support and sponsorship

Key Research and Development Program of Shandong (2015GSF118126), Young and Middle-Aged Scientists Research Awards of Shandong Province (BS2013YY010).

#### Conflicts of interest

There are no conflicts of interest.

**Zhao-Xia Zhang, Bao-Qi Yang, Qing Yang, Mei Wu,  
Guang-Jin Wang**

Department of Dermatology, Shandong Provincial Institute of  
Dermatovenereology, Jinan, China

**Correspondence:** Dr. Guang-Jin Wang,  
Shandong Provincial Institute of Dermatovenereology, Jinan,  
Shandong 250022, China.  
E-mail: wjg68@163.com

#### References

1. Criado PR, Criado RF, Avancini JM, Santi CG. Drug reaction with Eosinophilia and Systemic Symptoms (DRESS)/Drug-induced Hypersensitivity Syndrome (DIHS): A review of current concepts. *Am Bras Dermatol* 2012;87:435-49.
2. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, *et al.* Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: Does a DRESS syndrome really exist? *Br J Dermatol* 2007;156:609-11.
3. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. *Clin*

*Pharmacol Ther* 1981;30:239-45.

4. Harman KE, Morris SD, Higgins EM. Persistent anticonvulsant hypersensitivity syndrome responding to ciclosporin. *Clin Exp Dermatol* 2003;28:364-5.
5. Zuliani E, Zwahlen H, Gilliet F, Marone C. Vancomycin-induced hypersensitivity reaction with acute renal failure: Resolution following cyclosporine treatment. *Clin Nephrol* 2005;64:155-8.
6. Kirchoff MG, Wong A, Dutz JP. Cyclosporine treatment of drug-induced hypersensitivity syndrome. *JAMA Dermatol* 2016;152:1254-7.
7. Lee JH, Park HK, Heo J, Kim TO, Kim GH, Kang DH, *et al.* Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome induced by celecoxib and anti-tuberculosis drugs. *J Korean Med Sci* 2008;23:521-5.
8. Daoulah A, Alqahtani AA, Ocheltree SR, Alhabib A, Ocheltree AR. Acute myocardial infarction in a 56-year-old female patient treated with sulfasalazine. *Am J Emerg Med* 2012;30:638.e1-3.
9. Higa K, Hirata K, Dan K. Mexiletine-induced severe skin eruption, fever, eosinophilia, atypical lymphocytosis, and liver dysfunction. *Pain* 1997;73:97-9.
10. Lee SP, Kim SH, Kim TH, Sohn JW, Shin DH, Park SS, *et al.* A case of mexiletine-induced hypersensitivity syndrome presenting as eosinophilic pneumonia. *J Korean Med Sci* 2010;25:148-51.
11. Shiohara T, Kano Y, Takahashi R, Ishida T, Mizukawa Y. Drug-induced hypersensitivity syndrome: Recent advances in the diagnosis, pathogenesis and management. *Chem Immunol Allergy* 2012;97:122-38.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Access this article online	
<b>Quick Response Code:</b>	<b>Website:</b> www.ijdv1.com
	<b>DOI:</b> 10.4103/ijdv1.IJDVL_1084_16

**How to cite this article:** Zhang ZX, Yang BQ, Yang Q, Wu M, Wang GJ. Treatment of drug-induced hypersensitivity syndrome with cyclosporine. *Indian J Dermatol Venereol Leprol* 2017;83:713-7.

**Received:** January, 2017. **Accepted:** June, 2017.

© 2017 Indian Journal of Dermatology, Venereology, and Leprology | Published by Wolters Kluwer - Medknow