What should we know about drug reaction with eosinophilia and systemic symptoms?

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Definition and pathogenesis

Drug reaction with eosinophilia and systemic symptoms (DReSS) is a serious hypersensitivity drug reaction with multiorgan involvement. It occurs between 3 weeks and 3 months after the introduction of the culprit drug. However, a retrospective study reported a rapid onset of DReSS within 2 weeks of exposure¹. The drugs most commonly related to this condition are carbamazepine, allopurinol, and sulfasalazine. Interestingly, some drugs have been related to specific organ damage, such as allopurinol to kidney damage; minocycline to lung injury; and minocycline and sulfonamides to heart disease.

Before the recognition of the anticonvulsant hypersensitivity syndrome² in the 1980s, skin reactions were named after the culprit drug. Since the first DReSS acronym and diagnostic criteria were proposed in 1996, the Japanese Research Committee on Severe Cutaneous Adverse Reaction and the RegiSCAR group published modified diagnostic criteria and a scoring system, respectively. More recently, it was proposed to use a lower case “e” (DReSS) to represent eosinophilia since this might be not be seen until a later course or might not be present at all³.

DReSS is a T-cell-mediated hypersensitivity reaction; nevertheless, its pathogenesis is not completely clear. It is known that human leukocyte antigen subtypes are linked to certain drugs and specific ethnicity and that viral

reactivation is associated with a severe clinical presentation and disease flares. About the latter, it is demonstrated that the Treg and Th17 cells play a role in the herpesviruses reactivation and that differentiation of Treg into Th17 cells is associated with clinical resolution⁴.

Diagnosis and management

DReSS diagnosis is made based on the diagnostic criteria previously mentioned (Table 1). Prodromal symptoms are fever (present in 90% of cases), pruritus, lymphadenopathies, and dysphagia. During the acute phase, the most common symptom is a typically symmetrically distributed polymorphic skin eruption that tends to involve >50% of the body surface area. Facial edema is frequently seen, and mucosal involvement may be present.

The organs most commonly affected are the liver, kidney, and hematologic system. Liver enzymes are increased in up to 70% of patients, and the development of severe hepatitis increases the risk of mortality⁵. Furthermore, eosinophilia is a frequently reported sign in this condition, although its appearance may be delayed.

Management focuses on the withdrawal of the suspicious culprit drug and supportive care. For severe cases, systemic corticosteroids are the mainstay treatment option. It is recommended to monitor the course of the disease with viral assessment in those cases.

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Table 1. Diagnosis and management of DReSS

Diagnosis criteria		
Bocquet 1996	Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) group	RegiSCAR 2007 Inclusion criteria for potential case of DReSS
If three or more criteria:	If all the seven criteria: typical DIHS. If the first five criteria: atypical DIHS	^Hospitalization + Reaction suspected to be drug related + ≥ 3 of:
1. Cutaneous drug eruption	1. Maculopapular rash developing > 3 weeks after starting therapy with a limited number of drugs	1. Acute skin rash
2. Hematologic abnormalities eosinophilia $\geq 1.5 \times 10^9/L$ or presence of atypical lymphocytes	2. Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug	2. Fever > 38°C
3. Systemic involvement adenopathies ≥ 2 cm in diameter or hepatitis (liver transaminases $\geq 2 \times$ normal) or interstitial nephritis or interstitial pneumonitis or carditis	3. Fever > 38°C	3. Enlarged lymph nodes ≥ 2 sites
	4. Liver abnormalities (ALT > 100 U/L) or other organ involvement, such as renal involvement	4. Involvement of ≥ 1 internal organ
	5. Leukocyte abnormalities (at least one present) a. Leukocytosis ($> 11 \times 10^9/L$), b. Atypical lymphocytosis ($> 5\%$), c. Eosinophilia ($> 1.5 \times 10^9/L$)	Blood count abnormalities 5. Lymphocytes above or below the laboratory limits 6. Eosinophils above the laboratory limits (in percentage or absolute count) 7. Platelets below the laboratory limits
	6. Lymphadenopathy	
	7. Human herpesvirus 6 reactivation	
Management		
All cases	Withdrawal of suspected culprit drug Supportive care Multidisciplinary evaluation Monitoring of the course of the disease	
Mild cases	Symptomatic treatment, topical corticosteroid, H1 antihistamines	
Moderate-to-severe cases	Systemic corticosteroids (equivalent 1 mg/kg/day of prednisone) with a slow taper over 3-12 months Alternative treatments: cyclosporine; IVIG; mycophenolate mofetil; systemic corticosteroids with IVIG at a dose of 2 g/kg over 5 days Viral antibody titers and viral loads should be assessed at 1-2-week intervals Antiviral therapy is recommended if viral reactivation is confirmed	

^: potential cases should be classified as definite, probable, possible or no case. based on the scoring system for classifying DReSS cases.

Adapted from: Martinez-Cabriales SA, et al.³

DReSS is potentially fatal with a mortality rate of approximately 10%; however, these data may not be accurate since many cases are unregistered. Moreover, its prognosis is unpredictable and long-term monitoring should be done to assess for autoimmune diseases or end-organ failure.

Conflicts of interest

The author declares that they have no conflicts of interest.

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