The pitfalls associated with "DRESS" in sepsis.

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Abstract

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or Drug-Induced Hypersensitivity Syndrome (DIHS) is a severe drug reaction characterized by fever, rash, lymphadenopathy, hematological abnormalities, multiple organ failure, and viral reactivation. DRESS/DIHS is characterized by a delayed onset of severe symptoms after drug exposure, the persistence of symptoms after drug discontinuation, and similarity to symptoms of several other diseases, including infectious diseases, requiring an accurate diagnosis and management.

Keywords: DRESS, DIHS, Vancomycin, Sepsis.

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Description

ADRESS/DIHS is a severe drug reaction characterized by fever, rash, lymphadenopathy, hematologic abnormalities, multiple organ failure, and viral reactivation.

The prevalence of DRESS/DIHS is 2.18 [1] to 9.63 [2] per 100,000 hospitalized patients. In a retrospective study, the mortality rate was reported to be 3.8% [2] to 10% [3], and the causes of death were multiple organ failure, liver failure, shock, alveolar hemorrhage, and sepsis [3]. Allopurinol, carbamazepine, minocycline, and vancomycin are the most frequently reported causative agents [3,4]. The clinical manifestations of DRESS/DIHS are fever, rash, lymphadenopathy, hypereosinophilia, the appearance of atypical lymphocytes, and multiple organ involvement. The rash begins as an edematous rash on the face and progresses to diffuse erythema. Organ damage is seen in 85–96% of patients [4,5] and can occur in almost any organ, with the liver (75%), kidneys (37%), and lungs (32%) being the most commonly involved organs [6]. Liver damage is often reversible, but can progress to liver failure requiring transplantation, and is the leading cause of death in DRESS/DIHS [5]. It has also been suggested that the clinical features of DRESS/DIHS may vary depending on the causative agents. Vancomycin is strongly associated with renal impairment, and one retrospective study reported that 75% of patients with vancomycin-related DRESS/DIHS had renal impairment [6]. The degree of renal impairment ranges from mildly elevated creatinine to severe interstitial nephritis.

The exact etiology of DRESS/DIHS is still unknown, but drug-specific immune responses and viral reactivation are thought to be important factors. The administration of certain drugs activates CD4 T cells, causing an allergic reaction, followed by the emergence of CD8 T cells that target virus-infected cells [7]. In addition to HHV-6, the reactivation of HHV-7, EB virus, and cytomegalovirus has also been reported to be associated with the development of DRESS/DIHS. In addition to HHV-6, the reactivation of HHV-7, EB virus, and cytomegalovirus has been reported to be associated with the development of DRESS/DIHS [8,9]. Furthermore, it has been observed that during the acute phase of DRESS/DIHS, regulatory T cells proliferate, thereby activating the virus, and after the acute phase, regulatory T cells decrease, which may be involved in the subsequent development of delayed autoimmune sequelae [10,11]. Autoimmune sequelae occur in 11% of patients [12], with autoimmune thyroiditis being the most common; the development of type I diabetes, autoimmune hemolytic anemia, scleroderma, and systemic lupus erythematosus have been reported [13]. Genetic factors have also been implicated in familial predisposition to develop DRESS/DIHS, and effective prevention in high-risk populations may be possible in the future [14].

The diagnostic criteria for DRESS/DIHS have been proposed by the RegiSCAR group in Europe for DRESS (Table 1) and by J-SCAR in Japan for DIHS (Table 2). Comparing the two, it is possible that DRESS and DIHS are not separate but part of the same disease spectrum, and that DIHS identifies patients with a more severe status [15,16]. Although the presence of these diagnostic criteria supports the identification of patients with DRESS/DIHS, an accurate diagnosis and management are necessary because the relevant symptoms are similar to those of several other diseases, including infectious diseases, and symptoms appear late after the use of the causative agents. Therefore, there is a need to identify diagnostic markers for this disease. While TARC [17] and HMGB1 [18] are considered to be good candidates, they have not been fully validated.

Table 1: *Scoring system for classifying DRESS cases as definite, probable, and possible or no case.*

Item		Present		Absent
Fever ≧ 38.5℃		0		-1
Enlarged lymph nodes (>1 cm size, at least two sites)		1		0
Eosinophilia: ≧ 700 or ≧ 10 percent	≧ 1500 or ≧ 20 percent	1	2	0
Atypical lymphocytes		1		0
Rash ≧ 50 percent of body surface area		1		0
Rash suggestive (≧ 2 of facial edema, purpura, infiltration, desquamation)		1		0
Skin biopsy suggesting alternative diagnosis		-1		0
Organ involvement: one	two or more	1	2	0
Disease duration >15 days		0		-2

Investigation for alternative cause (blood cultures, ANA, serology for Hepatitisviruses, mycoplasma, chlamydia) ≧ 3 done and neative	1	0
*__Note:__ Total score <2: no case; 2-3: possible; 4-5: probable; ≧ 6: define.		

Table 2: *Diagnostic criteria of DIHS.*

S.no	Major findings
1	Rash occurs late onset from using culprit drug and expands rapidly
2	Prolonged for more than 2 weeks after stopping culprit drug
3	Fever ≧ 38°C
4	Liver dysfunction
5	Haematological features; one or more of the following features a. Leukocytosis (11000/ mm3) b. Atypical lymphocytes (more than 5%) c. Eosinophilia (1500/ mm3)
6	Enlarged lymph nodes
7	Reactivation of HHV-6
*__Note:__ Typical DIHS; All of 1 to 7 are applicable Atypical DIHS; 1 to 5 are applicable (4 is able to replace to another organ dysfunction)	

The treatment of DRESS/DIHS is aimed at identifying and stopping the causative agent, controlling the immune response to the virus, and preventing viral replication. Identifying the causative agent can be difficult, especially for patients who are taking multiple medications. Furthermore, discontinuation of the suspected causative agent does not immediately improve the patient's clinical condition. However, it is of utmost importance to identify any high-risk drugs that the patient may be taking. In such cases, the difference in the incubation period between exposure to the drug and the onset of symptoms may help in making the diagnosis. One retrospective study reported that the median incubation period for vancomycin-related DRESS/DIHS was 20 days, which was shorter than that of carbamazepine (33 days) and allopurinol (30 days) [19]. To determine the causative drug, a patch test in vivo and a Drug-Induced Lymphocyte Stimulation Test (DLST) in vitro were performed 6 months after the clinical symptoms disappeared. Cabanas et al. reported that DLST has higher sensitivity and specificity than the patch test in DRESS/DIHS [20]. The administration of systemic corticosteroids (0.5-2.0 mg/kg/day) is recommended for the control of the immune response, with slow tapering of the dose over several months. In more severe cases, concomitant high-dose immunoglobulin therapy may be considered [21]. With regard to viruses, reactivation of HHV-6 and 7 is short-lived and does not require antiviral drugs. However, CMV reactivates following HHV-6, causing multiple organ failure and a severe status; thus, antiviral therapy is recommended [22].

For those of us working in intensive care, sepsis is a common disease. However, patients with sepsis are said to become immunosuppressed due to a compensated anti-inflammatory syndrome at 1-2 weeks after the initial infection, and the mortality rate of secondary infections during this period is very high, requiring accurate diagnostic and therapeutic strategies.

In the course of sepsis, DRESS/DIHS is a condition that is difficult to distinguish from secondary sepsis because the administration of the causative antibiotic causes the virus to reactivate due to immunosuppression from the proliferation of regulatory T cells, resulting in symptoms such as fever and multiple organ damage, which occur later than drug exposure.

We believe that the concept of DRESS/DIHS is essential knowledge for those of us who treat sepsis; however, it is also a pitfall in our daily practice.

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