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Short Communication

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ANTIBIOTIC-ASSOCIATED "DRESS" SYNDROME: MALEFICENT DRESS?

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare reaction to certain medications, including antibiotics. It involves primarily a widespread skin rash, fever, swollen lymph nodes, and characteristic blood abnormalities such as an abnormally high level of eosinophils. Treatment consists of stopping the offending medication and providing supportive care. Systemic corticosteroids are commonly used.

Keywords: DRESS syndrome, Drug reaction, Skin rash, Fever, Eosinophilia, corticosteroids.

INTRODUCTION

"DRESS" syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) is an acronym for adverse reaction and is used to explain a hypersensitivity reaction. The acronym "DRESS" was introduced by Bocquetand Callout in 1996 (Bocquet *et al.,*1996; Callot and Roujeau, 1996) and unlike other drug allergic reactions, the clinical presentation of "DRESS" syndrome may be continued for several days or weeks even after stopping the suspected drug. (1)"DRESS" syndrome is one of the most severe adverse drug reactions which may be life-threatening with mortality rates reaches around 10%.(Eshki *et al*., 2009; Seth, 2008; Chiou *et al.,* 2008) Actually, "DRESS" syndrome is a severe, idiosyncratic multisystem reaction to a drug. The pathogenesis of DRESS syndrome is not well-known and is postulated to result of a complex interaction between culprit drug, genetic and viral factors. (Choquet-Kastylevsky *et al. 1998;* Knowles *et al.,* 2000) Shiohara et a. observed that sequential reactivations of several herpes viruses (HHV-6, HHV-7, EBV, and CMV) can be detected concurrently with the "DRESS" syndrome(Kano and Shiohara, 2004; Shiohara and Kano, 2007)and the pattern of the herpes virus family re-activation was similar to graft-versus-host disease (GVHD)(Peyriere *et al., 2006*) "DRESS" syndrome has various clinical presentations. The clinical manifestations often appear 2 to 8 weeks after introduction of the culprit drug.(Seth, 2008; Rzany *et al., 1999*)Common features consist of fever, rash, lymphadenopathy, hematological findings (eosinophilia, leukocytosis, mononucleosis, thrombocytopenia) and abnormal liver function tests. The skin manifestations are various but, typically consist of an urticarial, maculopapular eruption and, in some instances, vesicles, bullae, pustules, purpura, target lesions, facial edema, cheilitis, and erythroderma (Peyriere *et al.,* 2006; Eshki *et al.,* 2009) If "DRESS" syndrome is suspected, treating physician has to look systemically, because the extent of skin involvement does not always correlate with the extent of visceral organs involvement.(Seth, 2008) Of note, Visceral involvement (hepatitis, pneumonitis, myocarditis, pericarditis, nephritis, and colitis) is the major cause of morbidity and mortality in this syndrome. (Eland *et al.,* 1999) Diagnosis if "DRESS" syndrome may be difficult due to the different presentations. Symptoms such as rash, fever, and organ involvement are not specific and long- time between initiation of culprit drug and appearing of signs and symptoms brings more diagnostic difficulties. At least three diagnostic criteria have been created for proper diagnosis and assessment of DRESS syndrome:(Walsh and Creamer, 2011) RegiSCAR (The European Registry of Severe Cutaneous Adverse Reactions) criteria (2007) include at least 3 of the following 7 characteristics: (Eshki *et al.,*2009; Kardaun *et al., 2007*)

- skin eruption
- fever (>38°C)
- lymphadenopathy at least 2 sites
- involvement of at least 1 internal organ
- lymphocytosis (>4×103/μL) or lymphocytopenia (<1.5×103/μL)
- blood eosinophilia (>10% or 700/μL)
- thrombocytopenia (<120×103/μL)

Bocquet's criteria (1996) require meeting the following 3 features: (Seth, 2008)

- skin eruption
- blood eosinophilia (>1.5×103/μL) or the presence of atypical lymphocytes
- internal organ involvement, including lymphadenopathies (>2 cm in diameter), hepatitis (liver transaminases values > twice the upper normal limit), interstitial nephritis, and interstitial pneumonia or credits.

Japanesecriteria(2006) include the following features: (Shiohara *et al.,* 2007)

- maculopapular rash developing >3 weeks after starting a limited number of drugs
- prolonged clinical symptoms 2 weeks after discontinuing the causative drug
- fever (>38°C)
- elevation of liver enzyme (alanine aminotransferase [ALT] >100 U/L) or involvement of other organs

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- leukocytosis (>11×103/μL), atypical lymphocytosis (>5%) or eosinophilia (>1.5×103/μL)
- lymphadenopathy,
- human herpes virus (HHV)-6 reactivation.

In Japanese criteria the diagnosis of typical "DRESS" requires the presence of all 7 criteria.(Shiohara *et al.,* 2007) The most important differential diagnosis of "DRESS" syndrome including other cutaneous drug reactions such as Stevens Johnsons Syndrome (SJS) and toxic epidermal necrolysis (TEN).It is important to note that the clinical presentation of "DRESS" syndrome may mimic ongoing sepsis, and consideration of alternative diagnoses such as "DRESS" beside sepsis is crucial for optimal outcomes. (Blumenthal *et al.,* 2012) Treatment of "DRESS" syndrome needs early recognition followed by immediate cessation of all suspected drugs. (Santiago et al., 2010; Garcia-Doval *et al.,* 2000) Then supportive care is advised including local and systemic treatments. Systemic corticosteroids have been used for treatment of "DRESS" syndrome with dramatic response in majority of reports. Systemic corticosteroids may need to be continued for several weeks, with gradual tapering of the dosage. (Claire-Audrey *et al.,* 2010*;* Zain Husain *et al.,* 2013*;* Roujeau and Stern, 1994)Intravenous immunoglobulin (PonnusamySanthamoorthy *et al., 2012;* Nufar Marcus et al., 2018) and immunomodulators, such as cyclosporine, may also be used (Zuliani *et al., 2005;* Harman et al., 2003)

Conclusion

DRESS is a challenging drug adverse reaction which can cause life-threatening organ dysfunction. Clinicians must be alert to this possibility to reach the correct diagnosis and institute the appropriate management.

Conflict of interest

No

Table 1: Antibiotic-induced "DRESS" syndrome: Prevalence and end-organ damage (27)

Antibiotic class	DRESS Prevalence	Most common culprit Antibiotic in the class	Commonly involved	Comment
Penicillins	< 10%	Piperacillin/tazobactam co-amoxiclav	Liver	
Cephalosporins	4%	third-generations	liver	
Carbapenems	1.2%	Meropenem	liver	
Fluoroquinolones	2%	levofloxacin	Undetermined	
Aminoglycosides	0.8%	streptomycin	liver	
Glycopeptides	18%	Vancomycin > teicoplanin	Kidney > Liver > Lung	- HLA-A*32:01 is severely associated with vancomycin-induced DRESS. (28) - Allergic cross-reactivity between vancomycin and teicoplanin has been reported infrequently. (29) Thus, hypersensitivity to vancomycin is not a contraindication to the use of teicoplanin if it was necessary. (30)
Daptomycin	Undetermined	*	Undetermined	
Sulfonamides	9%	cotrimoxazole	liver	It seems that no cross-reactivity occurred between different sulfonamides regarding "DRESS" syndrome.(31)
Dapsone	Undetermined	*	liver	In non-leprosy patients, the HLA-B*13:01 allele was severely associated with dapsone-induced "DRESS" syndrome. (32)
Tetracyclines	8.3%	Minocycline	Liver, Kidney, Lung, Myocardium Lymph nodes	there is a possibility of tetracycline cross-reactivity with DRESS, and any tetracycline including tigecycline should be avoided in patients with a history of tetracycline-associated "DRESS" syndrome. (33)
Macrolides	0.8%	Azithromycin	Undetermined	
Lincosamide	1.2%		liver	
nitrofurantoin	1.2%	*	liver	
Linezolid	Undetermined	*	Undetermined	
Metronidazole	Undetermined	*	Undetermined	
Antituberculosis	42%	Rifampin > isoniazid > ethambutol > pyrazinamide	liver	Antituberculosis drugs could not be reintroduced until after the eosinophilia, rash, and toxic hepatitis had almost resolved.
Antiretrovirals	Considerable	Abacavir, nevirapine	liver > lung	Individuals expressing the HLA-B57:01 serotype have a higher incidence (55%) of developing "DRESS" syndrome in response to abacavir. (34) Individuals with HLA-DRB1:01:01 & 01:02, HLA-Cw4, HLA-B35 and HLA-C04 serotype have higher incidences of developing the syndrome in response to nevirapine. (35)
Anti-hepatitis C	Undetermined	Boceprevir, telaprevir	liver	
Anti- malaria	Undetermined	Quinine	Undetermined	
Anti-helminths	Undetermined	levamisole	Undetermined	

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