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REVIEW ARTICLE

Cardiac involvement in DRESS syndrome

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Abstract

Objective: Cardiac involvement in drug rash with eosinophilia and systemic symptoms (DRESS) syndrome varies considerably between 4% and 21%. Here we present our case and review literatures for its diagnosis and management. An algorithm for diagnosis of cardiac involvement in DRESS syndrome is proposed in this article.

Data sources: Data regarding DRESS-associated myocarditis and eosinophilic myocarditis were gather primarily from MEDLINE database.

Results: DRESS syndrome is a hypersensitivity reaction which is due to massive T cell stimulation resulting in cytotoxicity and eosinophil activation and recruitment. It is characterized by fever, morbilliform rash, and various systemic symptoms, in particular hepatitis. Hypersensitivity myocarditis (acute eosinophilic myocarditis) which is typically related to a drug reaction can lead to acute necrotizing eosinophilic myocarditis, cardiac thrombosis and fibrotic stage. Cardiac symptoms range from no symptoms to cardiogenic shock. Diagnosis is based on history, clinical findings, cardiac biomarkers and cardiac imaging techniques. Endomyocardial biopsy is done in a minority of patients for definite diagnosis. If suspected, drug discontinuation and suppression of immune reactions are the first therapies. Corticosteroids are the cornerstone of systemic treatments *and should be initiated at the time of diagnosis of DRESS syndrome*. Additional therapy and ventricular assist devices could be considered in refractory cases.

Conclusions: According to its high morbidity and mortality, patients with DRESS syndrome should be carefully monitored or screened for cardiac involvement. Multidisciplinary care is important for a successful treatment outcome.

Keywords: Drug rash with eosinophilia and systemic (DRESS) symptoms, cardiac involvement, pathogenesis, diagnosis, treatment

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Introduction

Adverse drug reactions are often classified into 2 major types which are Type A and Type B reactions. Type A reactions are more common (80%) and are mediated by the known pharmacologic and toxic effects of the drug including overdose, off target activities and drug interactions.[1] These reactions are dose-related and predictable. On the other hand, type B reactions are hypersensitivity reactions which are due to stimulation of immune and inflammatory cells. They can be classified as allergic, p-i (pharmacological interaction with immune receptors) and pseudo-allergic reactions.[2,3]

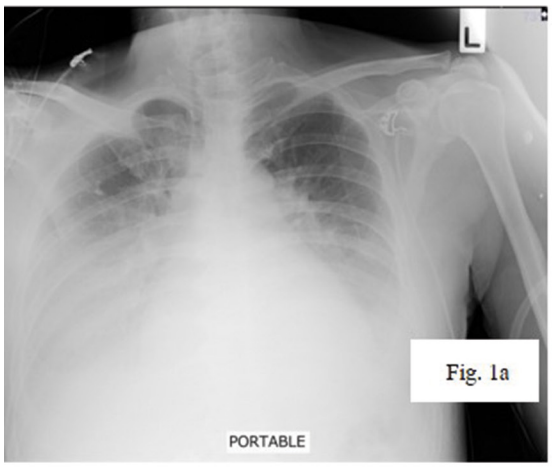
Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, also called drug-induced hypersensitivity syndrome, seem to be p-i reactions and are frequently linked to certain HLA-alleles e.g. abacavir, carbamazepine or allopurinol bind to certain HLA-alleles directly and thus elicit allo-like immune reactions.[2] One could categorize DRESS as Gell and Coombs type IV or delayed-type hypersensitivity reaction, consisting of activated T cells with cytotoxic activities (type IVc) and IL-5, IL-14/IL-13 producing T cells, which results in hyper-eosinophilia (type IVb).

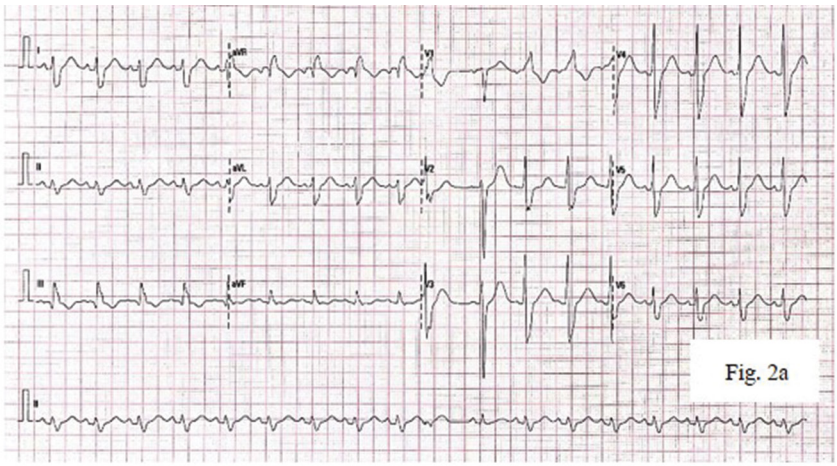
A retrospective analysis in Asian patients with DRESS showed that clinical presentations in Asian population did not differ from previous studies in Caucasian patients.[4] DRESS is characterized by fever, morbilliform eruption, and systemic involvements after exposure to an offending drug. Liver is the most common organ involvement.[4] Cardiac involvement was

described in two case series with 1/27 (4%) and 5/24 (21%) of patients.[4,5] To draw attention to this important and potentially fatal complication of DRESS, we present an own case and review its pathogenesis, clinical manifestations, diagnosis, and treatment, emphasizing that this systemic severe drug hypersensitivity reaction requires an interdisciplinary care.

Case

A 58-year-old male was admitted to Buddhachinaraj Hospital, Phitsanulok, Thailand due to a skin rash. He had underlying diseases of hypertension and chronic kidney disease which had been treated with amlodipine for 3 years. One month before admission, he was diagnosed with acute gouty arthritis. Colchicine 0.6 mg/day and allopurinol 100 mg/day were started for 30 days and 19 days, respectively before he developed facial edema and generalized erythematous macules and papules on his trunk and extremities. On admission, he had fever (T = 38.2˚C) and hepatomegaly. His pulse rate and blood pressure were in normal limits. There was no superficial lymphadenopathy and other systems were unremarkable. Laboratory investigations revealed eosinophilia (eosinophil 14%, absolute eosinophil counts 1,109/μL) but there was no atypical lymphocytosis. Serum creatinine level did not change from baseline (baseline creatinine 2.19 mg/dl). Stool examination was also done to exclude other causes of eosinophilia which revealed no parasitic infestations. Due to a history of drug exposure, facial edema and skin rash, allopurinol induced-DRESS syndrome was suspected. He was initially treated with topical corticosteroids and antihistamine. All possible offending drugs (allopurinol and colchicine) were discontinued.





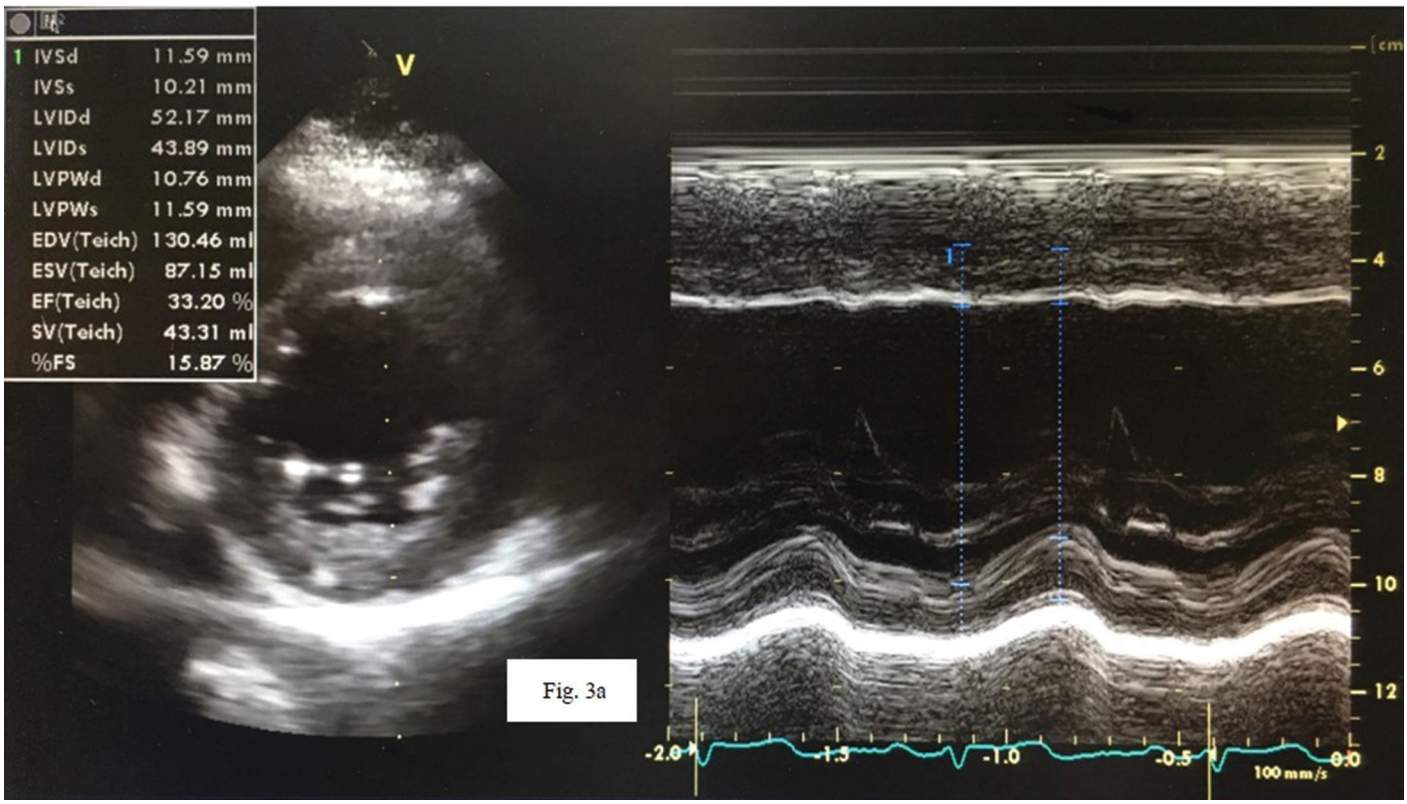


Figure 1. Chest-X-ray, electrocardiography, and echocardiography of the patient

Two days after admission, he developed acute dyspnea (respiratory rate 28 breaths/minute), hypotension (blood pressure 90/60 mmHg), tachycardia (pulse rate 120 beats/minute) and orthopnea but he did not have chest pain. Chest radiography indicated mild cardiomegaly with pulmonary congestion (**Figure 1a**). Sinus tachycardia without ST-T change was detected by an electrocardiography (ECG) (**Figure 1b**). An echocardiogram revealed generalized severe left ventricular dysfunction with left ventricular ejection fraction (LVEF) of 28% (**Figure 1c**). Cardiac biomarkers showed creatinine kinase (CK)-MB of 125 U/L (normal range: 0-40 U/L), troponin–T level of 48 ng/ml (normal range: 0-14 ng/ml), and N-terminal pro-hormone of basic natriuretic peptide (NT-proBNP) of 2,230 pg/ml (normal range: NT-proBNP <125 pg/mL). Although the complete criteria of DRESS syndrome were not fulfilled,[6-8] DRESS-associated myocarditis and congestive heart failure was suspected. Systemic corticosteroid (dexamethasone) with a dose of 1 mg/kg/day was started intravenously to decrease eosinophil infiltrations in myocardial tissue. Diuretic drug (furosemide) and inotropic agent (dobutamine) were used to treat congestive heart failure. After two days of treatment, he had an improvement in his clinical conditions. Dobutamine could be discontinued and furosemide could be administered orally. A repeat NT-proBNP analysis showed a drop from 2,230 pg/ml to 750 pg/ml. Coronary angiography showed normal coronary artery. Dexamethasone with a dose of 1 mg/kg/d was changed to prednisolone 1 mg/kg/d (60 mg/d) on day 5th of treatment. During hospitalization, prednisolone 60 mg/d was gradually tapered (60 mg/d for 3 days, 55 mg/d for 4 days, 50 mg/d for 4 days, 45 mg/d for 3 days) to 45 mg/d over a 2-week period. The patient recuperated completely and all cardiac biomarker levels (CK-MB, troponin-T, and NT-proBNP) returned to normal.

After three weeks of hospitalization, he was discharged with a prednisolone dosage of 40 mg/d. for 2 weeks. On day 35th of steroid treatment, he was followed at the cardiac outpatient clinic of Buddhachinaraj Hospital. There were no signs and symptoms in the flare-up of skin and cardiac conditions. Then, prednisolone was decreased gradually by 10 mg/month for 3 months (30 mg/d for 1 month, 20 mg/d for 1 month, and 10 mg/d for 1 month). The patient remained stable during a follow-up period at cardiac outpatient clinic. Prednisolone was stopped after 5 months of its initiation. An echocardiogram at month 6th revealed an improvement in LV function with a LVEF of 52%.

Discussion

Pathogenesis of DRESS syndrome

The pathogenesis of DRESS syndrome is only partially understood. It has been proposed to be a T cell-mediated reaction that relates to an individual with specific HLA haplotypes. There are 2 possible mechanisms that are believed to activate T cell reactions in drug allergy. First, the hapten/prohapten hypothesis: a drug that is not chemically reactive is metabolized to be a reactive drug metabolite (a hapten) and binds covalently to a self-peptide resulting in a new composite antigen (**Figure 2a**). This new peptide-hapten complex acts as antigen and binds to HLA, where it is then presented to the T cell receptor (TCR).[9-11] Second, the pharmacologic interaction hypothesis (p-i concept): a chemically inert drug can activate T-cell mediated reaction by binding directly and non-covalently to the immune receptors (i) HLA; (ii) TCR; or, rarely (iii) both HLA and TCR leading to a T cell activation, cytokine production, proliferation, and/or cytotoxicity (**Figure 2b**).[3,9-11] The direct drug binding to the HLA molecule in p-i reactions could explain the HLA predisposition, as drug binding with relevant affinity to the protein might be restricted to certain HLA-alleles only, e.g. of abacavir to HLA-B*57:01 only. Such HLA-linked p-i reactions have been documented for abacavir, carbamazepine, dapsone, flucloxacillin and allopurinol/oxypurinol, and were found to be

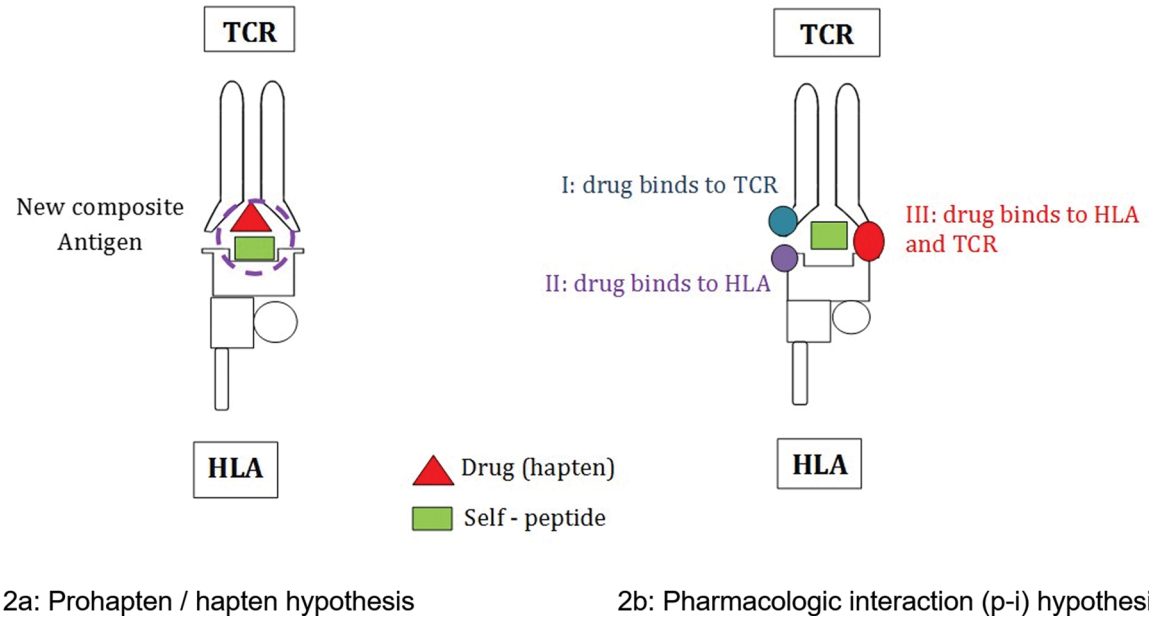


Figure 2. Two possible mechanisms that are believed to activate T cell reactions in drug allergy.

associated with severe reactions like Stevens-Johnson syndrome (SJS) / Toxic epidermal necorlysis (TEN), DRESS and others. A controversial issue is the altered peptide repertoire hypothesis, which was described only for abacavir, but not for other drugs.[10,11]

Pathogenesis of cardiac damage in DRESS syndrome

An immune alteration and production of cytokines such as granulocyte macrophage colony-stimulating factor, interleukin (IL)-13 and IL-5 in DRESS syndrome (type IVb) stimulate eosinophil production.[12,13] The degree of cardiac damage is associated with the duration of eosinophilia, the degree of eosinophilia (particularly > 5,000 /mm^3), and eosinophil activation.[14] However, why the eosinophils home to the cardiac tissue is unknown.

Eosinophilic cytoplasm contains specific and non-specific eosinophilic granules. Specific eosinophilic granules (cationic proteins) such as major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase are cardio-toxic agents.[15] These cardio-toxic agents, especially major basic protein and eosinophil cationic protein, can cause platelet activation, impairment of anticoagulant effects, and endothelial cell damage.[15,16] First, the infiltration of eosinophils in myocardial tissue change normal myocardial function. The degranulation of eosinophils within the myocardium leads to cell necrosis and apoptosis. Thrombus formation is developed later due to the binding of cationic proteins of eosinophils to the anion-binding exosite of thrombomodulin.[13] The final stage is fibrotic scarring of cardiac endothelium and valves resulting in a non-compliant ventricle.[14,17]

Cardiac biopsies may reveal an inflammatory cell infiltrate, which is dominated by eosinophils and lymphocytes, like in DRESS associated hepatitis.[18,19] Thus, cytotoxic T cells may contribute to damage of cardiac tissue directly.

Clinical features

Prodromal symptoms of DRESS such as pruritus and fever may precede cutaneous eruptions by several days.[20] Cutaneous manifestations can be various and usually occur between 2 and 6 weeks after the first exposure to the culprit drug.[20] However, a diffuse morbilliform rash which is the most common presentation and initially presents on the face, upper aspect of the trunk, and upper extremities, is characteristic.[20] Prominent facial edema especially in the periorbital and midfacial areas mimicking angioedema can be found. The diagnosis of DRESS syndrome depends on a history of drug use, clinical presentations, and laboratory investigations. The diagnostic criteria of DRESS syndrome are shown in **Table 1**. Accordingto European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR), acute rash, drug-related reaction, and hospitalization in combination with 3 of the 4 following criteria including (i) fever > 38 ˚C, (ii) lymphadenopathy involving at least 2 sites, (iii) at least 1 internal organ involvements e.g. liver, renal, and *heart*, and (iv) hematologic abnormalities (eosinophilia and lymphocytosis) are necessary for diagnosis. For Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR), seven criteria are

Table 1. Three proposed diagnostic criteria for drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

	Bocquet et al[6]	RegiSCAR[7]	J-SCAR[8]
Requirement for diagnosis	≥ 3 criteria	≥ 3 criteria of the following asterisk marks	all 7 criteria = typical 5 asterisk marks = atypical
History		- hospitalization - reaction suspected to be drug related	- prolonged clinical symptoms after discontinuing the causative drugs *
Fever		- fever ≥ 38˚C *	- fever ≥ 38˚C *
Cutaneous finding	- drug eruption	- acute rash	- macular rash developing 3 weeks after starting offending drug *
Hematologic abnormalities	- eosinophilia > 1.5×10^9/L or atypical lymphocytosis	one of the following hematologic abnormalities * - eosinophilia over laboratory limits - lymphocyte count over and under normal limits - thrombocytopenia under laboratory limits	one of the following hematologic abnormalities * - leucocytosis (>11×10^9 /L) - atypical lymphocytes (>5%) - eosinophilia (>1.5×10^9 /L)
Other organ involvements	- lymphadenopathy ≥ 2 cm in diameter - hepatitis with liver transaminases ≥ 2 times of the normal values - interstitial nephritis - interstitial pneumonitis - carditis	- lymphadenopathy involving ≥ 2 sites * - at least 1 internal organ involvement *	- lymphadenopathy - liver abnormalities (ALT > 100 U/L) *
Viral reactivation			- HHV-6 reactivation

Abbreviations: Regiscar, The European Registry of Severe Cutaneous Adverse Reaction; J-SCAR, Japanese Research Committee on Severe Cutaneous Adverse Reaction; HHV-6, human herpes virus-6

needed to diagnose *typical* DIHS, referred to as DRESS syndrome. The seven criteria include (i) maculopapular rash developing 3 weeks after starting causative drug, (ii) prolonged clinical symptoms after discontinuing the causative drug, (iii) fever > 38 ˚C, (iv) liver or other organ abnormalities, (v) leukocyte abnormalities, (vi) lymphadenopathy, and (vii) HHV-6 reactivation.[6-8] Our case had fever, a morbilliform rash, facial edema and eosinophilia after allopurinol usage which were compatible with the diagnosis of DRESS syndrome according to RegiSCAR criteria.[7]

Eosinophilic infiltrations of myocardial tissue can lead to 3 stages of cardiac pathology: (1) **an acute necrotic stage:** clinical presentations range from asymptomatic (typically) to a fulminant course. Symptoms can occur **immediately and up to 4 months** after the appearance of rash and fever.[21,22] Echocardiography is usually normal, although myocardial wall thickening may be found due to edema process. (2) **a thrombotic stage:** embolic phenomena such as strokes and ischaemic extremities can occur. Thrombi within the apices of the left ventricle or right ventricle or both can be identified by echocardiography.[14] (3) **a fibrotic stage:** patients may have left or right sided heart failure. At this stage, echocardiography may show restrictive cardiomyopathy or valvular regurgitation.[14] One can differentiate the acute stage into 2 forms, which are hypersensitivity myocarditis (acute eosinophilic myocarditis) and acute necrotizing eosinophilic myocarditis.

Hypersensitivity myocarditis is usually underdiagnosed as its clinical presentations can be various from asymptomatic to non-specific symptoms.[14] Moreover, it can be a self-limited condition after withdrawal of the offending drug and disappearance of immune activation.[21] Non-specific symptoms include tachycardia, low blood pressure, dyspnea, malaise, and chest pain.[14,21]

Acute necrotizing eosinophilic myocarditis is the more severe form and can be rapidly fatal. Patients can present with acute heart failure, cardiogenic shock, hypotension without any features of anaphylactic reaction, and chest pain.[21,22] A review of 22 cases of DRESS-associated myocarditis by Bourgeois et al. showed that the most common presenting symptom was **dyspnea (15/22), followed by tachycardia (13/22), hypotension (12/22), and chest pain (10/22)**, respectively.[21] Median survival of patients with acute necrotizing eosinophilic myocarditis is approximately 3-4 days.[21]

Diagnosis of cardiac involvement in DRESS syndrome

Several conditions that can cause eosinophilic infiltrations of endomyocardium and should be considered in the differential diagnosis. These include malignancies, hypereosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), parasitic infections, and transplant rejections. **Table 2** demonstrates prominent clinical features of DRESS-associated hypersensitivity myocarditis, HES, and Churg-Strauss syndrome.[23-25] Laboratory investigations such as bone marrow biopsy with tissue typing, serum anti-neutrophilic cytoplasmic antibodies (ANCA), serum myeloperoxidase -ANCA, and stool samples for parasites may be helpful to establish the diagnoses.

Due to a high mortality rate of cardiac involvement in DRESS syndrome, it is recommended to perform baseline cardiac screening tests such as ECG and echocardiography in all patients with DRESS syndrome. ECG may be unremarkable or shows sinus tachycardia, supraventricular tachycardia, non-specific ST segment, and T-wave changes. In acute stage, echocardiography probably demonstrates an increased left ventricular wall thickness due to interstitial myocardial edema. Thrombi may be identified within the apices of right or left

Table 2. Prominent clinical features of hypersensitivity myocarditis, idiopathic hypereosinophilic syndrome, and Churg-Strauss syndrome[23-25]

	DRESS- associated hypersensitivity myocarditis	Hypereosinophilic syndrome	Churg–Strauss syndrome
Diagnosis	Diagnose DRESS syndrome by criteria of Bocquet et al. or RegiSCAR or J-SCAR	Unexplained eosinophilia (>1,500/mm^3) for longer than 6 months with evidence of organ damage	≥ 4 of the following criteria - asthma - eosinophilia of more than 10% in peripheral blood - paranasal sinusitis - pulmonary infiltrates (may be transient) - histological proof of vasculitis with extravascular eosinophils - mononeuritis multiplex or polyneuropathy
Initial presentations	Pruritus, fever and rash	Skin lesions and dyspnea (pulmonary involvement), followed by gastrointestinal involvement.	Allergic inflammation of the upper airways with asthma and/or polyps
Common skin lesions	Morbilliform eruptions	Erythematous pruritic maculopapular and nodular eruptions, angioedema, urticaria	Palpable purpura, subcutaneous nodules
Cardiac features	Dyspnea and tachycardia It can occur immediately or within 4 months after rash.	Heart failure (75%) and dyspnea (50%) Clinical course is typically indolent.	Acute pericarditis with slight pericardial effusion is a typical manifestation.

puberty, and body habitus.[28,29] Cardiac magnetic resonance imaging with delayed enhancement sequences is very efficient to visualize focal endomyocardial lesions.[30] **Figure 3** demonstrates our proposed algorithm to investigate cardiac involvement in DRESS syndrome. In our case, ECG and coronary angiogram results excluded acute myocardial infarction. Echocardiography and NT-proBNP level indicated left ventricular dysfunction. Based on the clinical setting and all laboratory results, systemic corticosteroid was initiated to treat as DRESS-associated myocarditis rather than doing endomyocardial biopsy.

Endomyocardial biopsy is a gold standard to identify cardiac pathology but it is an invasive and regretfully not very sensitive technique. Therefore, it has been done in a minority of patients or post-mortem. Histopathology of cardiac involvement in DRESS syndrome can reveal eosinophilic infiltration of the endocardial tissue and subendocardial interstitium. Myocardial necrosis and eosinophilic granulomas are sometimes found.[14,21,22,31]

Treatment

Early diagnosis and withdrawal of the offending drug are the most important steps in management of DRESS. In case of cardiac involvement patients should be treated and monitored closely in an intensive care unit by multidisciplinary team specialized in dermatology, cardiology, and cardiothoracic surgery. Treatment of acute eosinophilic myocarditis is aimed to rapidly lower eosinophil infiltrations in myocardial tissue and to suppress immune activation.[14,20,21] The early administration of systemic corticosteroids with a minimum dose of 1.0 mg/kg/day of prednisolone or equivalent has been proposed to be a first-line treatment. Systemic corticosteroids can inhibit the degranulation of eosinophils and decrease a risk of myocardial necrosis.[14,20,21] However, the risks and benefits of systemic corticosteroids are still debatable.[14,32-34] Generally, a significant ventricles in a thrombotic stage. A left ventricular dysfunction with wall motion abnormalities may be found.[14] Cardiac biomarkers include CK-MB, troponin T, and NT-proBNP, all of which should be investigated in patients who have cardiac symptoms. If the levels of CK-MB and troponin-T are not increased in patients who developed chest pain, acute coronary syndrome is less likely. An elevated NT-proBNP level is usually found in patients with acute dyspnea from cardiac origin rather than pulmonary cause.[26,27] It is proposed that an increased NT-proBNP level is related to left ventricular dysfunction and can be used to assess long-term morbidity of myocarditis.[5,26,27] One has to consider that normal values vary by age, gender, improvement of symptoms can be found within several days after initiating steroid treatment. A relapse may occur if

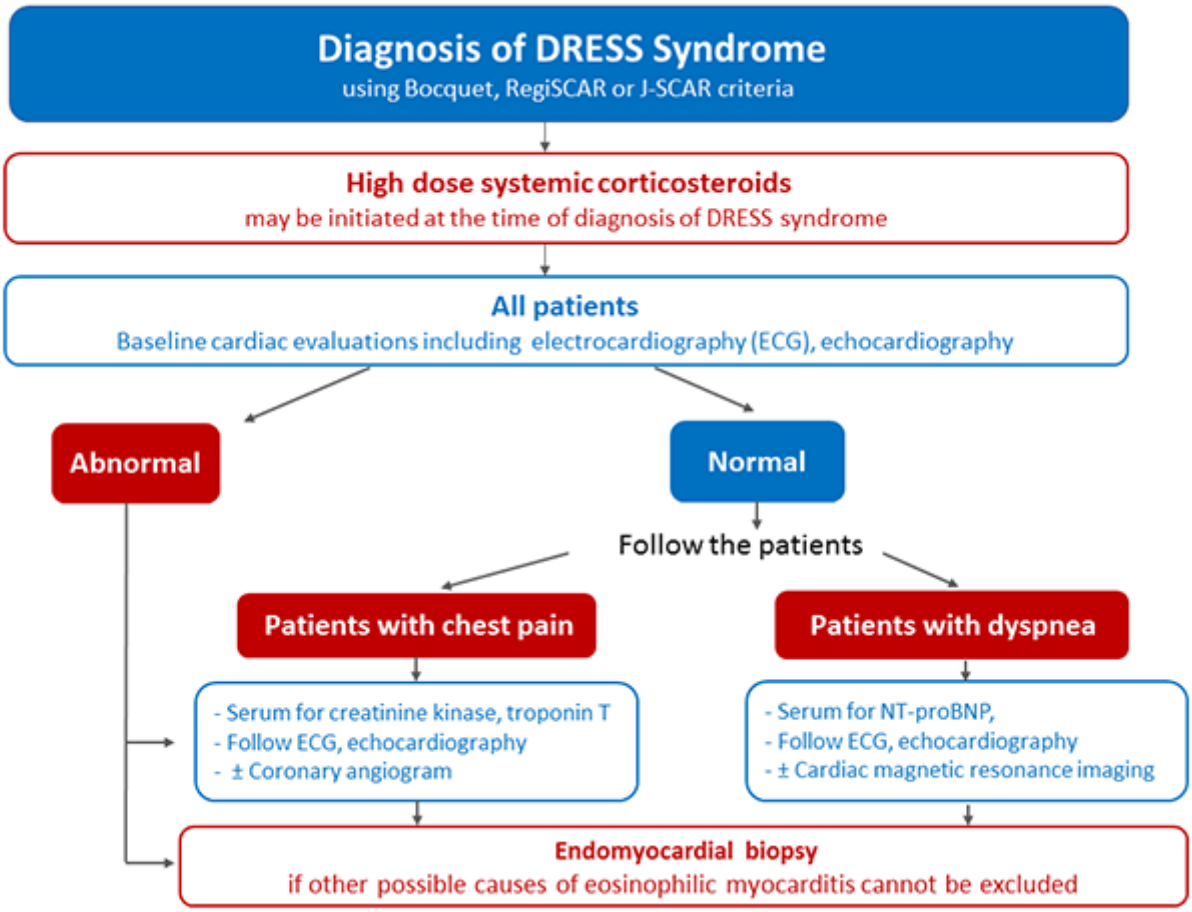


Figure 3. An algorithm to diagnose cardiac involvement in drug rash with eosinophilia and systemic symptoms (DRESS) syndrome

Abbreviations: Regiscar, The European Registry of Severe Cutaneous Adverse Reaction; J-SCAR, Japanese Research Committee on Severe Cutaneous Adverse Reaction;

corticosteroids are too rapidly reduced. Therefore, systemic corticosteroids should be gradually tapered over 3 to 6 months after clinical condition is stable.[21,31-36] A course of pulsed methylprednisolone, 30 mg/kg intravenously for 3 days, can be administered. An adjunctive high dose of intravenous immunoglobulin (IVIG) therapy is controversial and is not generally recommended, as the high-viscosity property of IVIG may rapidly deteriorate cardiac function in myocarditis. Accordingly, IVIG is not recommended to use as a monotherapy in DRESS syndrome or DRESS-associated myocarditis.[31,38,39] Plasmapheresis and immunosuppressive drugs such as azathioprine, mycophenolate mofetil, muromonab-CD3, cyclosporine, rituximab have been reported to be used as an adjunctive therapy for DRESS-associated myocarditis.[21,31,35] No report exist yet about the use anti-IL-5 antibody in DRESS with myocarditis (mepolizumab). Although both ventricles are typically affected and there is an increased risk of ventricular arrhythmias in DRESS-associated myocarditis, prophylaxis with anti-arrhythmic agents are not recommended. Alternatively, patients should be carefully monitored and treated immediately after developing arrhythmias. Supportive therapy such as fluid restriction, diuretics, angiotensin-converting enzyme inhibitor, and beta-blocker should be considered to prevent decompensated heart failure. Ventricular assist device implantation, intra-aortic balloon pumping, and extracorporeal membrane oxygenation support have been used successfully as a transitional device in cases of refractory heart failure, refractory hypotension and fulminant myocarditis.[21,22]

Conclusions

Patients with DRESS syndrome should be carefully monitored or screened for eosinophilic myocarditis: signs of cardiac involvement in DRESS syndrome are elevation of cardiac biomarkers, changes of electrocardiography, changes in echocardiography such as thrombi and ventricular dysfunction. Some patients need cardiac magnetic resonance imaging and possibly cardiac biopsies to confirm the diagnosis. Multidisciplinary care is important for a successful treatment outcome.

References

1. Wheatley LM, Plaut M, Schwaninger JM, Banerji A, Castells M, Finkelman FD, et al. Report from the National Institute of Allergy and Infectious Diseases workshop on drug allergy. J Allergy Clin Immunol 2015;136: 262-71.
2. Pichler W, Adam J, Watkins S, Wuillemin N, Yun J, Yerly D. Drug Hypersensitivity: How Drugs Stimulate T Cells via Pharmacological Interaction with Immune Receptors. Int Arch Allergy Immunol 2015;168:13-24
3. Pichler WJ. Pharmacological interaction of drugs with antigen-specific immune receptors: the p-i concept. Curr Opin Allergy Clin Immunol. 2002;2:301-5.
4. Ang CC1, Wang YS, Yoosuff EL, Tay YK. Retrospective analysis of drug-induced hypersensitivity syndrome: a study of 27 patients. J Am Acad Dermatol. 2010;63:219-27.
5. Ben m'rad M, Leclerc-Mercier S, Blanche P, Franck N, Rozenberg F, Fulla Y, et al. Drug-induced hypersensitivity syndrome: clinical and biologic disease patterns in 24 patients. Medicine (Baltimore). 2009;88:131-40
6. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg. 1996;15:250-7.
7. 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
8. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol. 2007;156:1083-4
9. Pichler WJ. Delayed drug hypersensitivity reactions. Ann Intern Med. 2003;139:683-93
10. Ostrov DA, Grant BJ, Pompeu YA, Sidney J, Harndahl M, Southwood S, et al. Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. Proc Natl Acad Sci U S A. 2012;109:9959-64.
11. Illing PT, Vivian JP, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. Nature. 2012;486:554-8.
12. Picard D, Janela B, Descamps V, D'Incan M, Courville P, Jacquot S, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. Sci Transl Med. 2010;2:46ra62.
13. Séguéla PE, Acar P. Hypereosinophilic heart disease. In: da Cruz E, Ivy D, Jaggers J, editors. Pediatric and congenital cardiology, cardiac surgery and intensive care. London: Springer-Verlag; 2014.p. 2439-51.
14. Séguéla PE, Iriart X, Acar P, Montaudon M, Roudaut R, Thambo JB. Eosinophilic cardiac disease: Molecular, clinical and imaging aspects. Arch Cardiovasc Dis. 2015;108:258-68.
15. Rothenberg ME. Eosinophilia. N Engl J Med. 1998;338:1592-600.
16. Sano K, Kobayashi M, Sakaguchi N, Ito M, Hotchi M, Matsumoto K. A rat model of hypereosinophilic syndrome. Pathol Int. 2001;51:82-8.
17. Gottdiener JS, Maron BJ, Schooley RT, Harley JB, Roberts WC, Fauci AS. Two-dimensional echocardiographic assessment of the idiopathic hypereosinophilic syndrome. Anatomic basis of mitral regurgitation and peripheral embolization. Circulation. 1983;67:572-8.
18. Zhang SN, He QX, Yang NB, Ni SL, Lu MQ. Isoniazid-induced Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Presenting as Acute Eosinophilic Myocarditis. Intern Med. 2015;54:1227-30.
19. Mennicke M, Zawodniak A, Keller M, Wilkens L, Yawalkar N, Stickel F, et al. Fulminant liver failure after vancomycin in a sulfasalazine-induced DRESS syndrome: fatal recurrence after liver transplantation. Am J Transplant. 2009;9:2197-202.
20. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. J Am Acad Dermatol. 2013;68:693.e1-14.
21. Bourgeois GP, Cafardi JA, Groysman V, Hughey LC. A review of DRESS-associated myocarditis. J Am Acad Dermatol. 2012;66:e229-36.
22. Lo MH, Huang CF, Chang LS, Kuo HC, Chien SJ, Lin IC, et al. Drug reaction with eosinophilia and systemic symptoms syndrome associated myocarditis: a survival experience after extracorporeal membrane oxygenation support. J Clin Pharm Ther. 2013;38:172-4
23. Ito K, Hara H, Okada T, Terui T. Hypereosinophilic syndrome with various skin lesions and juvenile temporal arteritis. Clin Exp Dermatol. 2009;34:e192-5.
24. Kleinfeldt T, Nienaber CA, Kische S, Akin I, Turan RG, Körber T, et al. Cardiac manifestation of the hypereosinophilic syndrome: new insights. Clin Res Cardiol. 2010;99:419-27.
25. Jeong HC, Kim KH, Cho JY, Song JE, Yoon HJ, Seon HJ, et al. Cardiac involvement of Churg-Strauss syndrome as a reversible cause of dilated cardiomyopathy. J Cardiovasc Ultrasound. 2015;23:40-3.
26. Maries L1, Manitiu I. Diagnostic and prognostic values of B-type natriuretic peptides (BNP) and N-terminal fragment brain natriuretic peptides (NT-pro-BNP). Cardiovasc J Afr. 2013;24:286-9.
27. Nasser N, Perles Z, Rein AJ, Nir A. NT-proBNP as a marker for persistent cardiac disease in children with history of dilated cardiomyopathy and myocarditis. Pediatr Cardiol. 2006;27:87-90
28. Mlczoch E, Darbandi-Mesri F, Luckner D, Salzer-Muhar U. NT-pro BNP in acute childhood myocarditis. J Pediatr. 2012;160:178-9.
29. Nir A, Lindinger A, Rauh M, Bar-Oz B, Laer S, Schwachtgen L, et al. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. Pediatr Cardiol. 2009;30:3-8.
30. Chun W, Grist TM, Kamp TJ, Warner TF, Christian TF. Images in cardiovascular medicine. Infiltrative eosinophilic myocarditis diagnosed and localized by cardiac magnetic resonance imaging. Circulation. 2004;110:e19.
31. Ginsberg F, Parrillo JE. Eosinophilic myocarditis. Heart Fail Clin 2005;1: 419-29.

32. Husain Z, Reddy BY, Schwartz RA, DRESS syndrome: Part II. Management and therapeutics. J Am Acad Dermatol. 2013;68:709.e1-9
33. Aslan I, Fischler M, Laser KT, Haas NA. Eosinophilic myocarditis in adolescent: a case report and review of the literature. Cardiol Young 2013;23:277-83.
34. May LJ, Patton DJ, Fruitman DS. The evolving approach to paediatric myocarditis: a review of the current literature. Cardiol Young 2011;21: 241-51.
35. Al Ali AM, Straatman LP, Allard MF, Ignaszewski AP Eosinophilic myocarditis: case series and review of literature. Can J Cardiol. 2006;22: 1233-7.
36. Ho CH, Uzunyan MY. Myocarditis in drug rash with eosinophilia and systemic symptoms. Cardiol Young. 2015;25:1210-3
37. Shaughnessy KK, Bouchard SM, Mohr MR, Herre JM, Salkey KS. Minocycline-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with persistent myocarditis. J Am Acad Dermatol. 2010;62:315-8.
38. Kito Y, Ito T, Tokura Y, Hashizume H. High-dose intravenous immunoglobulin monotherapy for drug-induced hypersensitivity syndrome. Acta Derm Venereol 2012;92:100-1.
39. Joly P, Janela B, Tetart F, Rogez S, Picard D, D'Incan M, et al. Poor benefit/risk of balance of intravenous immunoglobulins in DRESS. Arch Dermatol 2012:148:543-4.