

Drug reaction with eosinophilia and systemic symptoms in a cohort of Asian children

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Abstract

Background/objectives: Drug reaction with eosinophilia and systemic symptoms (DRESS) is rare but potentially fatal in children. Fever and rash, which are salient features of DRESS, may mimic other commonly encountered pediatric conditions. We profiled the DRESS cases in a tertiary children's hospital in Singapore.

Methods: The medical records of all pediatric DRESS patients diagnosed from 2006 to 2016. Data on epidemiology, inciting drugs, clinical, pathologic manifestations, and treatment were assessed.

Results: Ten patients aged 4-16 years old were diagnosed with DRESS within the 10-year period. Drugs implicated were antibiotics, such as trimethoprim-sulfamethoxazole, and anticonvulsants, such as carbamazepine, phenobarbitone, and levetiracetam. All patients had fever and pruritic exanthems. Desquamation, purpura, and oral mucositis were also observed. Lymphadenopathy, hepatomegaly, and facial edema occurred frequently. There was liver involvement in all cases, but none progressed to liver failure. Seven patients had eosinophilia, and nine had atypical lymphocytosis. Other laboratory abnormalities included low hemoglobin, thrombocytosis, and prolonged coagulation times. All patients received systemic corticosteroids of varying durations and dosages. Systemic steroids were weaned after 19 days to 4 months. Disease resolution, with liver enzyme levels returning to normal, occurred within 28-90 days. One patient developed TSH-receptor-antibody-positive hyperthyroidism 6 months after the onset of DRESS, while another patient developed chronic urticaria 4 months after resolution of DRESS.

Conclusion: Early recognition of DRESS is important to ensure that the inciting drug is discontinued, and supportive treatment started expediently. Liver involvement was very common but responded well to systemic steroids.

KEYWORDS

DRESS (drug reaction with eosinophilia and systemic symptoms), drug reaction, eosinophilia, pediatric drug reaction, systemic symptoms

1 | INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug hypersensitivity syndrome (DHS), is a rare but severe cutaneous adverse reaction. Its manifestations include

extensive mucocutaneous rash, lymphadenopathy, fever, hepatitis, hematological abnormalities with eosinophilia and atypical lymphocytes, and possibly other organ involvement.¹ DRESS has been reported to occur in all age groups but is less common in children than adults.² The incidence of DRESS in the general population is

estimated to range from one case per 1000 drug exposures to one in 10 000 exposures.^{3,4} Drugs most commonly associated with DRESS include anticonvulsants, allopurinol, sulfonamides, nonsteroidal antiinflammatory drugs (NSAIDs), minocycline, and antiretrovirals.^{1,5,6} Systemic steroids are most commonly used in the treatment of DRESS, but there are no randomized controlled trials or observational studies evaluating the efficacy of the various treatments for DRESS, especially in the pediatric population.⁷ Accurate and prompt diagnosis of DRESS in the pediatric age group may be challenging, as the two salient clinical features, fever and rash, are common manifestations of other childhood illnesses, for example viral infections.⁸ Our study aims to retrospectively analyze the epidemiology, clinical

features, investigations, management and long-term outcome of DRESS in a cohort of children in our tertiary pediatric hospital.

2 | METHODS

We performed a retrospective analysis of pediatric patients diagnosed with DRESS at KK Women's & Children's Hospital from 2006 to 2016. Cases were identified by relevant International Classification of Disease (ICD) codes from inpatient records. Data regarding the epidemiology, clinical features, laboratory investigations, treatment, and outcomes were reviewed. A diagnosis of DRESS was

TABLE 1 Characteristics of patients with DRESS

Patient no.	Age/Race/Sex	Inciting drug	Onset (d)	Manifestations	Transaminitis	Eosinophilia	Atypical Lymphocytes
1	14/C/M	Bactrim	28	Fever, rash, facial edema, jaundice, lymphadenopathy	+	-	+
2	11/C/F	Bactrim	28	Fever, rash, facial edema, lip swelling, hepatomegaly, lymphadenopathy	+	+	+
3	13/I/M	Bactrim and augmentin	42	Fever, rash, lymphadenopathy, hepatomegaly, abdominal pain, myalgia	+	+	+
4	11/C/F	Carbamazepine	12	Fever, rash, lip erosions, lymphadenopathy	+	+	-
5	8/C/M	Phenobarbitone	21	Fever, rash, facial edema, lymphadenopathy, drowsiness, rotatory nystagmus	+	+	+
6	13/C/M	Sulfasalazine	28	Fever, rash, facial edema, lymphadenopathy, hepatomegaly	+	+	-
7	16/C/F	TCM	18	Fever, rash, lymphadenopathy, pleural effusion, hepatomegaly	+	+	+
8	17/C/M	Phenobarbitone	5	Fever, rash, hepatomegaly, lymphadenopathy	+	-	+
9	4/I/M	Carbamazepine	42	Fever, rash, hepatomegaly, epigastric pain, ascites	+	+	+
10	5/Ca/M	Levetiracetam	28	Fever, rash, lip swelling	+	+	-

Ca, Caucasian; C, Chinese; DOI, day of illness; HC, hydrocortisone; I, Indian; IV, intravenous; LFT, liver function test; LOS, length of stay; MP, methylprednisolone; mo, months; ND, not done; PNL, prednisolone; TRab+, thyroid receptor antibody positive; PO, per oral; TCM, traditional Chinese medicine; HHV-6 PCR, human herpes virus 6 polymerase chain reaction; +, present; -, absent.

^aTailed down early by patient NB: Patient was previously already on PO PNL 2 mg/kg/d for Anti-NMDA receptor antibody encephalitis and due to this, PO PNL was tailed down over 8 months before switching to mycophenolate mofetil.

based on a combination of cutaneous and systemic manifestations of DRESS. We regarded a European Registry of Severe Cutaneous Reactions (RegiSCAR) score of 4 and above as fulfilling the criteria for probable-to-definitive diagnosis of DRESS. The study was approved by our hospital's central ethics review committee (CIRB).

3 | RESULTS

3.1 | Demographic data

Ten patients with DRESS were identified (Table 1) over the 10-year study period. There were six boys and four girls, and their ages

ranged from 4 to 17 years, with a mean of 11.2 years. Nine subjects were of Asian descent (six Chinese, two Indians, and one Indonesian-Chinese), and one was Caucasian.

3.2 | Causes

The most common drugs implicated were anticonvulsants and antibiotics. Inciting drugs were trimethoprim-sulfamethoxazole (three cases), carbamazepine (two), phenobarbitone (two), sulfasalazine (one), amoxicillin-clavulanic acid (one), and levetiracetam (one). One of these patients had received trimethoprim-sulfamethoxazole and amoxicillin-clavulanic acid concurrently. One patient had a reaction secondary to

HHV-6 PCR	DOI offending drug stopped	DOI diagnosis made	DOI treatment started	LOS (d)	Treatment started	Days to resolution with normal LFT	Sequelae
+	1	9	9	8	PO PNL 0.5 mg/kg/d with tailing dose over 2 mo	28	Chronic urticaria 4 mo later
ND	12	14	13	14	PO PNL 1.25 mg/kg/d with tailing dose over 3 wk ^a	56	-
ND	7	8	8	10	PO PNL 1 mg/kg/d for 1 d, switched to IV HC 4 mg/kg/d for 2 d when transaminitis worsened. Then PO PNL 1 mg/kg/d with tailing dose over 7 wk	49	-
-	2	3	3	7	PO PNL 0.27 mg/kg/d with tailing dose over 19 d	30	-
- (blood and cerebrospinal fluid)	11	11	12	16	IV HC 7.7 mg/kg/d for 11 d then PO PNL 1.5 mg/kg/d with tailing dose over 4 mo	90	-
ND	4	27	5	3	IV MP 11.2 mg/kg/d for 3 d, then PO PNL 1.36 mg/kg/d with tailing dose over 4 mo	29	TRab+ hyperthyroidism 6 mo later
ND	8	15	15	7	PO PNL at 0.5 mg/kg/d, increased to 1 mg/kg/d when transaminitis worsened and dose tailed over 2 mo	49	-
ND	3	3	5	13	IV HC 5.5 mg/kg/d for 6 d then PO PNL 1.4 mg/kg/d with tailing dose over 39 d	36	-
-	5	5	5	18	IV 8.5 mg/kg/d for 6 d then PO PNL 1.2 mg/kg/d with tailing dose over 4 mo and 16 d	39	-
-	6	4	6	9	IV MP 30 mg/kg/d for 3 d then PO PNL 2 mg/kg/d ^{NB}	35	-

a traditional Chinese medication. The interval from commencement of drug to onset of symptoms ranged from 5 days to 6 weeks, with a mean duration of 25 days. Interestingly, patient 8, who developed DRESS secondary to phenobarbitone, had previously taken the same drug as an infant for 1 year without any adverse reactions. He developed DRESS 3 weeks after phenobarbitone was restarted at the age of 8 years. The diagnosis of DRESS in this patient was delayed because of this previously presumed tolerance to phenobarbitone.

3.3 | Clinical presentation

All patients presented with high fever and a generalized pruritic exanthem (Figures 1, 2, and 3). In addition, the rash in two patients was desquamative, one was purpuric, and five patients had oral mucositis. Facial edema was seen in four patients, lymphadenopathy in eight patients, and hepatomegaly in six patients. Other less common clinical findings included pleural effusion, ascites, abdominal pain, myalgia, and drowsiness. One patient was found to have persistent rotatory nystagmus.

3.4 | Laboratory investigations

Elevated liver enzymes were found in all subjects, with alanine aminotransferase (ALT) ranging from 88 to 1172 U/L (normal: 9-25 U/L) and aspartate aminotransferase (AST) ranging from 70 to 903 U/L (normal: 18-36 U/L). Five subjects had elevated alkaline phosphatases, ranging from 437 to 559 U/L. Seven subjects had abnormally elevated bilirubin levels. Of these, five had elevation of both direct bilirubin (range: 10-212 $\mu\text{mol/L}$, normal: 0-7 $\mu\text{mol/L}$) and total bilirubin levels (range: 29-294 $\mu\text{mol/L}$, normal: ≤ 14 $\mu\text{mol/L}$) and two had elevation of only direct bilirubin levels (range: 9-14 $\mu\text{mol/L}$). None of the patients progressed to overt liver failure. Seven patients had eosinophilia, with absolute eosinophil counts ranging from 0.78 to $3.74 \times 10^9/\text{L}$ (normal: $0-0.70 \times 10^9/\text{L}$) and the remaining three with normal eosinophil levels. Seven patients had low hemoglobin levels, ranging from 9.9 to 12.2 g/dL (Normal: 13-15.5 g/dL). Four patients had abnormal platelet levels, with one

having mild thrombocytopenia (platelet count $139 \times 10^9/\text{L}$, normal: $150-450 \times 10^9/\text{L}$) and three having thrombocytosis (platelet counts 471 557, $864 \times 10^9/\text{L}$). Nine patients had atypical lymphocytosis, ranging from 2% to 33%. Coagulation profile tests which included prothrombin time (PT) and partial thrombin time (PTT) were done for six patients, with abnormal results in two patients (Patient 2: PT: 25.2 seconds, INR: 1.97 and PTT 43.3 seconds; Patient 9 PT: 60.3 seconds, INR: 7.09 and PTT: 86.3 seconds). Blood human herpes virus 6 (HHV-6) PCR was performed in five patients, with only one positive result. Cerebrospinal (CSF) fluid HHV-6 PCR was negative in the patient with rotatory nystagmus. No patients had serological evidence of acute Epstein-Barr virus reactivation or infection. Five patients had thyroid function tests performed with normal results. None of our patients had abnormal renal function tests or urinalysis. One patient had sinus bradycardia attributed to hypokalemia secondary to intravenous hydrocortisone.

3.5 | Histopathological findings

Skin biopsy was performed in five patients. All five biopsies showed a superficial perivascular inflammatory cell infiltrate, consisting



FIGURE 2 Erythematous patches and papules affecting the limbs in DRESS

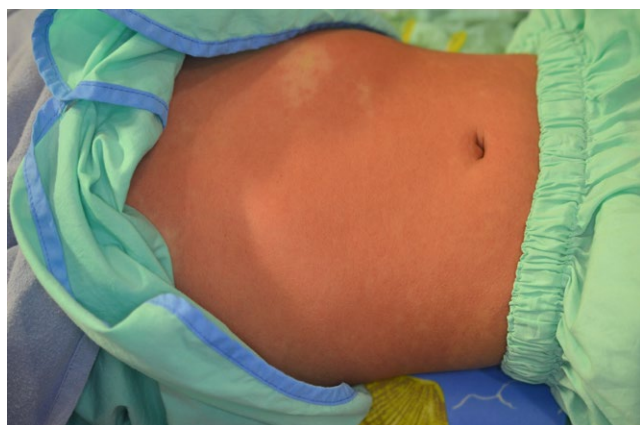


FIGURE 1 Generalized exanthem, with some areas of sparing, affecting the trunk in a case of DRESS



FIGURE 3 Erythematous patches and papules on the cheeks and lip swelling as manifestations of DRESS

mostly of lymphocytes and histiocytes. Eosinophils were present in two biopsies. Basal vacuolar alteration and apoptotic keratinocytes were present in three biopsies.

3.6 | Treatment outcomes and prognosis

All 10 patients were treated with systemic corticosteroids of varying durations and dosages. Two patients were treated with 3 days of pulsed methylprednisolone at 11.2 and 30 mg/kg/d, respectively, with the latter already on concomitant oral prednisolone for anti-NMDA (N-methyl D-aspartate) receptor antibody encephalitis. They were then continued on tapering courses of oral prednisolone. The remaining eight patients were treated with various combinations of intravenous hydrocortisone and oral prednisolone. Dosages ranged from 0.27 to 2 mg/kg/d of prednisolone equivalent. Patients were weaned off systemic steroids after a duration of between 19 days and 4 months (mean duration: 65 days). The speed of weaning depended on the patient's clinical response to treatment. There were no fatalities in our cohort. It took 28–90 days (mean duration: 44.1 days) for liver enzymes to reach normal levels after starting corticosteroids. One patient had a recurrence of DRESS after 20 days while still on tapering doses of oral prednisolone. Another patient had a recurrence 1 week after oral prednisolone was stopped after initial taper. Symptoms improved after the patient was restarted on a low dose of oral prednisolone at 0.13 mg/kg/d. With regard to long-term sequelae, one patient developed TSH-receptor-antibody-positive (TRAb+) hyperthyroidism 6 months after, and one patient developed chronic urticaria 4 months after resolution of DRESS.

4 | DISCUSSION

DRESS is a rare, but serious drug reaction that is less common in children than adults.² Common clinical manifestations of DRESS seen in our study were fever, generalized exanthems, and lymphadenopathy. The rash may progress to become desquamative,^{8,9} as seen in two of our patients. Desquamation is less commonly reported in adult patients.^{10,11} Facial edema, mucositis, and internal organ involvement, most commonly manifesting as elevated liver transaminases, are frequently encountered, similar to adult patients.^{8,12} Liver involvement is an equally common finding in both adults and children, affecting almost all patients. Renal involvement occurs more commonly in adults than children.¹ In our study, none of the patients developed renal impairment, while a study involving 16 pediatric DRESS patients had two patients with kidney involvement.¹³ Similar to our study, common laboratory findings reported in DRESS are elevated transaminases, eosinophilia, and atypical lymphocytosis.^{2,14} Atypical lymphocytosis can pose a significant diagnostic problem in pediatric patients (as well as young adults), as it is also seen commonly in infectious mononucleosis, an important differential diagnosis.

Drugs, immunologic defects, and infections, such as HHV-6, have been linked to the pathophysiology of DRESS. The detection

of HHV-6 infection or reactivation has even been proposed as a diagnostic marker for DRESS.³ Association between active HHV-6 and severe DRESS has been reported.^{15,16} There is postulation that HHV-6 may interfere with some of the enzymes responsible for drug detoxification.¹⁷ It is also hypothesized that HHV-6 reactivation results from an allergic immune response to a certain drug with an innate ability to stimulate T cells which may harbor latent HHV-6, and when stimulated by the drug, the viral genome is replicated and reactivated in the cell.¹⁸ The cytotoxic and immunomodulatory effects of HHV-6 may prolong disease course and increase disease severity.³ Only one patient in our cohort, a 14-year-old girl with DRESS secondary to trimethoprim-sulfamethoxazole, was found to be positive for HHV-6 reactivation. Her disease course, however, was not more severe, with her length of stay being 8 days, which was shorter than the average of 10.5 days. The time to normalization of her liver enzymes was 28 days, compared to the average of 44.1 days. However, the inciting drug in her case was stopped on day 1 of illness, the earliest of all the cases. This may have contributed to a less severe disease course.

The crucial initial step in management of DRESS is discontinuation of the inciting drug. Beyond this, there is a lack of consensus on definitive medical therapy for DRESS, and there are no controlled clinical trials. Nevertheless, the most widely accepted and used treatment is systemic corticosteroids.^{3,7,18,19} There are case reports of successful treatment with plasma exchange,²⁰ intravenous immunoglobulins,²¹ cyclosporine,²² and N-acetylcysteine.²³ All our patients were treated with either oral or intravenous corticosteroids, with two treated with intravenous pulsed methylprednisolone. These two patients showed good response with faster resolution of DRESS and normalization of liver enzymes compared to the rest of our patients.

One of the most common long-term complications of DRESS is autoimmune thyroid disease (Graves' disease, Hashimoto's thyroiditis, autoimmune thyroiditis, and painless thyroiditis).²⁴ Other immune and infectious sequelae have also been described. One patient in our cohort developed TSH-receptor-antibody-positive hyperthyroidism 6 months after resolution of the rash, and another developed chronic urticaria 4 months after resolution of DRESS. It is postulated that viral infection or reactivation and dysfunction of regulatory T cells during the resolution stage contributes to development of autoimmune diseases in DRESS patients.²⁵ Surveillance for new-onset diseases post-DRESS should be considered for all patients.

5 | CONCLUSION

DRESS is a rare but severe drug reaction, with many disease-mimickers, especially in the pediatric patient group. Physicians should have a high index of suspicion for diagnosis, ensuring that the inciting drug is discontinued and treatment started expediently. Although liver involvement was very common in our patients, it responded well to treatment with systemic steroids. There are no established guidelines for dosing and duration of systemic steroids

in children with DRESS. The use of topical corticosteroids also warrants further investigation. Although less common in children than adults, long-term sequelae, such as hypothyroidism, can occur and patients need to be monitored.

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