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DRESS Syndrome: Examples from the Pediatric Literature

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The acronym Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) was first used by Bocquet and colleagues in 1996 to describe patients exhibiting a drug-induced condition characterized by an extensive rash, fever, lymphadenopathy, hematologic abnormalities, hepatitis, and involvement of the kidneys, lungs, heart, or pancreas.¹ The onset of symptoms is often delayed, occurring 2-6 weeks after drug initiation. DRESS syndrome shares many characteristics in common with anticonvulsant hypersensitivity syndrome (AHS), also referred to as drug-induced hypersensitivity syndrome (DIHS), and appears to represent a variation in presentation rather than a distinctly different syndrome. The incidence of DRESS has been estimated to be between 1 in 1,000 and 1 in 10,000 drug exposures. It carries a mortality rate of 10-20%, with most fatalities the result of liver failure. Treatment consists of supportive therapy, corticosteroids, and antihistamines.²⁻⁴

Proposed Mechanisms

The pathogenesis of DRESS syndrome is not yet well understood. Although it is considered an idiosyncratic reaction, three potential causative factors have been identified among multiple cases: 1) a defect in drug metabolism resulting in the failure to eliminate toxic reactive intermediates, 2) reactivation of human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7), Epstein-Barr virus (EBV), or cytomegalovirus (CMV), which may serve as a trigger for the reaction, and 3) a genetic predisposition that alters immune response.¹⁻⁴

Based on these factors, Moling and colleagues successfully treated an adult with sulfasalazine-related DRESS using a combination of prednisone, N-acetylcysteine to neutralize reactive metabolites and reduce oxidative stress, and valganciclovir to reduce the effects of HHV-6 reactivation.⁵ Further work is needed to establish the efficacy of this novel combination and determine its potential role in the management of DRESS syndrome.

Diagnostic Criteria

Two groups have developed specific criteria for making the diagnosis of DRESS.^{4,6,7} The RegiSCAR program was developed by an international study group investigating severe cutaneous reactions (SCAR).⁷ To meet the definition of DRESS, patients must have three of the four main RegiSCAR criteria: an acute rash, fever above 38° C, lymphadenopathy at two sites, involvement of at least one internal organ, and abnormalities in lymphocyte and eosinophil counts. Additional criteria include hospitalization and that the reaction is suspected to be drug-related.

A Japanese consensus group has developed a second set of criteria for DRESS.⁷ The diagnosis requires meeting seven of the nine criteria in this system or all of the first five: a maculopapular rash developing > 3 weeks after drug initiation, clinical symptoms continuing > 2 weeks after stopping therapy, fever > 38° C, liver abnormalities (ALT > 100 IU/L) or other organ involvement, leukocytosis, atypical lymphocytes, eosinophilia, lymphadenopathy, or HHV-6 reactivation.

Drugs Associated with DRESS

More than 50 drugs have been linked to DRESS syndrome. The drugs most often reported with DRESS include anticonvulsants (particularly those with aromatic structures), sulfa derivatives, antidepressants, nonsteroidal anti-inflammatory drugs, and antimicrobials (Table).^{2,3,8}

Table. Drugs associated with DRESS in two or more cases

Abacavir	Lamotrigine
Allopurinol	Mexiletine
Amitriptyline	Minocycline
Captopril	Nevirapine
Carbamazepine	Oxcarbazepine
Cefixime	Phenobarbital
Celecoxib	Phenytoin
Dapsone	Sulfasalazine
Hydroxychloroquine	Sulfamethoxazole
Ibuprofen	Vancomycin

Recent Pediatric Case Reports

Phenytoin

Cases of both AHS and DRESS have been reported in children taking phenytoin. In 2009, Armin and colleagues described two cases.⁹ The first patient, a 7-year-old boy with a complex medical history including chronic renal failure, developed fever and a skin rash which persisted despite a month of antibiotics. His symptoms progressed to include lymphadenopathies and arthralgia, along with a mild anemia, leukopenia, and an elevated erythrocyte sedimentation rate (ESR). His symptoms failed to improve after stopping the antibiotics. Upon detailed review of the patient's history, it was discovered that he had started therapy with phenytoin 2 months earlier. A diagnosis of AHS was made and the phenytoin was discontinued. The fever and rash resolved within one week. At follow-up 3 weeks later, all symptoms had resolved and all laboratory tests were approaching normal values.

In the second case, a 5-year-old girl was admitted with a history of fever, rash, and lymphadenopathy for 2 weeks. She subsequently developed hepatosplenomegaly and severe respiratory distress with a parahilar infiltrate. Laboratory values indicated leukocytosis, eosinophilia, thrombocytopenia, increased transaminase levels, and an increased ESR. After a patient history revealed the use of phenytoin for the previous 1.5 months, a diagnosis of presumed DRESS was made and phenytoin was discontinued. Although administration of intravenous immune globulin early during her admission failed to produce improvement, treatment with methylprednisolone at the time when phenytoin was stopped resulted in significant benefit. Her fever, rash, and respiratory distress resolved within a week.

Two more pediatric cases of phenytoin-associated DRESS were published earlier this year. Gupta and colleagues described the case of a 16-year-old boy in *BMJ Case Reports*.¹⁰ The patient had been taking phenytoin 300 mg/day and folic acid 5 mg/day for 6 weeks. He presented with a high-grade fever, jaundice, and an erythematous rash that had been present for 15 days. The rash began as a maculopapular eruption, but progressed to an exfoliative dermatitis. Upon examination, he had generalized lymphadenopathy and tender hepatomegaly. Laboratory values included a hemoglobin of 12 g/dL and a leukocyte count of 15,700/mm³, with 15% eosinophils, 52% polymorphs, 28% lymphocytes, and 5% monocytes. Serum transaminases were greater than 5 times the upper limit of normal, with a serum bilirubin of 7.6 mg/dL. A biopsy of the rash revealed spongiosis with intraepidermal

vesiculation and patchy exocytosis. A diagnosis of DRESS was made, phenytoin was stopped, and prednisolone was started at a dose of 1 mg/kg/day. The patient's symptoms resolved within a week. Prednisolone was continued for 2 weeks, followed by a 4-week taper.

Deka and colleagues described a 10-year-old boy who developed a high fever, cough, respiratory distress, hoarseness, and a rash while taking clonazepam, gabapentin, and phenytoin.¹¹ His symptoms progressed to include oral mucosal ulceration, lymphadenopathy, periorbital and extremity edema, hepatomegaly, and rales. Laboratory values revealed eosinophilia and elevated serum transaminases. Antibiotic treatment with amoxicillin-clavulanic acid and vancomycin failed to produce improvement. A diagnosis of DRESS was made, phenytoin was discontinued, and steroid therapy was started. Within 48 hours, the patient defervesced and his symptoms began to resolve.

Carbamazepine and Oxcarbazepine

Buyuktiryaki and colleagues described DRESS in an 8-year-old girl taking carbamazepine.¹² The patient initially presented to an emergency department with fever, lymphadenopathy, and a rash on her trunk. She was given amoxicillin-clavulanic acid, acetaminophen, and hydroxyzine. Ten days later, she returned with no improvement. A detailed medication history revealed that the patient had been prescribed carbamazepine 5 weeks earlier. During her hospitalization, she developed cervical lymphadenopathy, a desquamating rash on the face, trunk, and extremities, and hepatosplenomegaly. Laboratory values included a leukocyte count of 6,200/ μ L with 22% eosinophils, 41% neutrophils, 29% lymphocytes, and 7% monocytes. Serum transaminases were within the normal range, but γ -glutamyl transferase was elevated at 296 IU/L. Her C-reactive protein was 7.5 mg/dL (normal < 0.8 mg/dL). Immunoglobulin and complement levels were normal. Bone marrow aspiration revealed dysplastic changes with 24% eosinophils.

After the patient failed to respond to antibiotics, a hypersensitivity reaction to carbamazepine was suspected. Skin biopsy revealed acanthosis, parakeratosis, and spongiosis in the epidermis, edema, and eosinophilic infiltration in the dermis. After meeting the RegiSCAR criteria for DRESS, the patient's carbamazepine was replaced with levetiracetam and a short course of systemic corticosteroids and an antihistamine were started. Symptoms resolved within 4 weeks. Six weeks after her recovery, the patient underwent patch testing to compare her reaction to carbamazepine, levetiracetam, and petroleum as a control. Carbamazepine produced a positive

response within 48 hours at both 5 and 10% concentrations. Levetiracetam and the control produced no response.

Oxcarbazepine, the keto homologue of carbamazepine, has been linked to DRESS in a single case report. In a 2004 issue of *Archives of Pediatrics*, Bosdure and colleagues described an 11-year-old girl with a cutaneous eruption, fever, and severe acute hepatitis associated with oxcarbazepine.¹³ It had been thought that oxcarbazepine would be less likely to produce DRESS because of its metabolic profile. Unlike carbamazepine, oxcarbazepine is cleared by renal excretion and undergoes only minimal hydroxylation.¹⁴ This case suggests that alterations in metabolic function may be a trigger for DRESS even with drugs not relying primarily on hepatic metabolism for elimination.

Naproxen and Sulfasalazine

Piñana and colleagues published a case of DRESS in an 11-year-old boy who was taking naproxen and sulfasalazine for the management of juvenile idiopathic arthritis.¹⁵ After one month of combination therapy (8 weeks after starting naproxen 250 mg twice daily and 4 weeks after the addition of sulfasalazine 500 mg twice daily), the patient was hospitalized with a rash, fever, facial edema, lymphadenopathy, jaundice, and hepatosplenomegaly. Within a week, he had progressed to acute hepatitis and renal tubular dysfunction. Laboratory tests revealed a leukocyte count of 22,500/mm³, with eosinophilia, a hemoglobin of 12.3 g/dL, with serum transaminases greater than 1,000 IU/L and a γ -glutamyltransferase of 1,972 IU/L (normal 5-65 IU/L). C-reactive protein was elevated at 3.1 mg/dL. Polymerase chain reaction (PCR) for HHV-6, IgG for parvovirus B19, IgG for CMV, and IgG anti-EBNA for EBV were all positive.

Both sulfasalazine and naproxen were discontinued and prednisone 2 mg/kg/day, along with an antihistamine, were started for presumed DRESS. Additional studies revealed no other source for his symptoms. A skin biopsy revealed spongiosis and necrotic keratinocytes, with inflammatory infiltrates. Bone marrow biopsy revealed hyperplasia of the eosinophil cell line. Within a week of starting supportive care, his symptoms began to improve. He was discharged after 3 weeks. Prednisone was tapered off over the next 2 months. At follow-up, he remained asymptomatic. While the development of DRESS in adults with autoimmune diseases has been reported by multiple authors, this is the first case documented in a child.

Antibiotics

In 2010, Orbak and colleagues described a case of DRESS in a 7-year-old girl taking penicillin

for an upper respiratory tract infection.¹⁶ The patient presented with a pruritic rash, fever, and periorbital and perioral edema. She had been prescribed oral penicillin V for tonsillopharyngitis 15 days earlier. After failing to improve, she was hospitalized and given IV penicillin for 2 days, followed by ceftriaxone for 4 days for continued fever. Her rash, fever, and fatigue continued to progress, with lymphadenopathy and edema. There were no signs of hepatosplenomegaly.

Laboratory studies revealed a leukocytosis of 31,100/ μ L with 16% eosinophils and atypical lymphocytes. Her hemoglobin was 13.8 g/dL. Lactate dehydrogenase was elevated (602 IU/L, normal 80-225 IU/L), as was γ -glutamyltransferase (36 mg/dL, normal < 30 mg/dL). Serum transaminases were within the normal range at admission, but increased throughout the first 10 days of admission. C-reactive protein was elevated at 1.2 mg/dL, with an ESR of 30 mm/h. The diagnosis of DRESS was made and antibiotics were discontinued. Treatment was initiated with glucocorticoids and antihistamines. Her symptoms began to resolve within 10 days, and by two months her laboratory values had returned to normal.

A case of probable cephalosporin-induced DRESS in a 3-year-old was published in 2008.¹⁷ The patient initially presented with protracted fever, elevated serum transaminases, and eosinophilia associated with severe acute hepatitis A infection. She then developed acute renal failure, occurring 8 weeks after the onset of her fever and eosinophilia. A renal biopsy demonstrated diffuse eosinophilic and lymphocytic infiltrates with necrotic tubular lesions, suggesting a potentially immunologic-mediated mechanism. Evaluation of the patient's medical history revealed the use of cefixime and sulfamethoxazole-trimethoprim 3 weeks prior to admission for her hepatitis A infection. The authors hypothesized that this case of DRESS represents a reaction to one or both of the antibiotics, triggered by the hepatitis A infection.

Nevirapine

There have been several reports of DRESS occurring in adults taking nevirapine, a nonnucleoside reverse transcription inhibitor for the treatment of human immunodeficiency virus (HIV). In 2007, Santos and colleagues reported the first case of nevirapine-induced DRESS in a child.¹⁸ They described a 12-year-old girl with perinatally-acquired HIV. Four months after being started on nevirapine as part of a highly active antiretroviral therapy (HAART) following virologic failure on her previous regimen, she developed fever, cough, a sore throat, nausea and vomiting, and respiratory distress. She was

treated for a presumed atypical pneumonia without improvement.

The patient's leukocyte count was 9,700/mm³ with 31% eosinophils. C-reactive protein and ESR were elevated at 13.5 mg/dL and 62 mm/h, respectively, and serum transaminases were increased. Testing for parvovirus IgG was positive, but parvovirus IgM and HHV-6 PCR were negative. Her antiviral regimen was held and IV immune globulin (2 g/kg) was administered. She became afebrile and her rash improved within 24 hours. One week later her HAART regimen was restarted and within 48 hours, her fever and rash returned. She was subsequently placed on a regimen without nevirapine, which she tolerated.

Summary

Although the mechanisms underlying DRESS syndrome remain poorly understood, there are a growing number of cases reported in children and adults that highlight the distinctive presentation of this hypersensitivity reaction. A diagnosis of DRESS syndrome should be considered in any patient with severe rash, fever, eosinophilia or lymphocytic changes. Prompt recognition, with supportive therapy and initiation of corticosteroids, may prevent or minimize additional organ system involvement.

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Formulary Update

The following actions were taken at the October meeting of the Pharmacy and Therapeutics Committee:

1. Triamcinolone acetonide (Triesence™) was added to the Formulary for the intravitreal treatment of ocular inflammatory conditions unresponsive to topical corticosteroids.
2. Ranibizumab 0.3 mg/0.05 mL (Lucentis®) was added for treatment of diabetic macular edema.
3. Ferric subsulfate (Monsel's solution) was added as a local hemostatic agent.
4. The restriction on bevacizumab (Avastin®) was amended to include use for patients with cerebral necrosis and edema secondary to fractionated radiation therapy or radiosurgery.
5. Buprenorphine/naloxone sublingual film (Suboxone®) was added for maintenance in patients taking this therapy prior to admission.
6. The restriction on inhaled nitric oxide (INOMax®) was amended to include use for patients with severe pulmonary hypertension with severe vasoplegia undergoing complex cardiac surgery as a second-line agent.

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