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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome in an Adolescent Girl With Epilepsy: A Case Report of Severe Multorgan Involvement

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but potentially life-threatening severe cutaneous adverse drug reaction characterized by a delayed onset of fever, extensive skin eruption, hematologic abnormalities, and internal organ involvement. Antiepileptic drugs are among the most frequently implicated medications. Early recognition and prompt withdrawal of the culprit drug with appropriate treatment are essential to prevent severe complications such as multiorgan failure. We report the case of a 15-year-old girl with autism spectrum disorder treated for uncontrolled epilepsy requiring multiple antiepileptic medications who developed severe DRESS syndrome seven to eight weeks after initiation of lamotrigine. The patient presented with mucocutaneous lesions with fever, eosinophilia, acute kidney injury, severe hepatocellular damage, respiratory manifestations, and a marked inflammatory response. DRESS was diagnosed using the RegiSCAR criteria. Carbamazepine and lamotrigine were immediately discontinued and replaced with levetiracetam. Systemic corticosteroid therapy at 1 mg/kg/day was initiated with supportive management. Despite an initial improvement, the patient's clinical condition deteriorated again, followed by fatal respiratory failure. This case highlights the diagnostic complexity and potentially fulminant course of pediatric DRESS, particularly when multiple systemic organs are involved, and urges clinicians to maintain a high index of suspicion for DRESS in children receiving aromatic antiepileptic drugs who develop fever and a generalized rash several weeks after treatment initiation.

Categories: Pediatrics, Allergy/Immunology, Dermatology

Keywords: antiepileptic drugs, carbamazepine, cutaneous adverse drug reaction, dress, drug hypersensitivity, eosinophilia, lamotrigine, multiorgan failure, pediatric dress

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome, is a rare and potentially fatal severe cutaneous adverse drug reaction. It is characterized by a delayed clinical presentation, usually occurring two to eight weeks after exposure to the culprit medication, followed by a combination of fever, extensive cutaneous eruption, facial edema, lymphadenopathy, hematologic abnormalities, and internal organ involvement [1,2].

DRESS is distinguished from other severe drug reactions by its prolonged and sometimes unpredictable course. The syndrome may persist or relapse after withdrawal of the offending drug or with viral reactivation, particularly human herpesvirus 6 (HHV-6), as well as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus 7 (HHV-7) [2,3]. Genetic predisposition and specific drug-related immune responses also appear to contribute to disease development [4].

A wide range of medications have been associated with DRESS including aromatic anticonvulsants, allopurinol, antibiotics, and antiretroviral agents [1,2]. Among children, antiepileptic medications are the most frequently implicated drugs in DRESS, which can manifest with extensive multisystem involvement and may lead to severe or life-threatening complications [5,6]. Diagnosis is primarily clinical and is supported by laboratory findings and exclusion of alternative diagnoses. The RegiSCAR scoring system is widely used to classify suspected cases as no, possible, probable, or definite DRESS [7,8]. Recent pediatric consensus recommendations emphasize on severity assessment in addition to diagnostic scoring and propose a pediatric-specific, severity-based therapeutic approach [6].

We report a fatal case of severe DRESS syndrome in a 15-year-old girl treated for epilepsy with lamotrigine and carbamazepine, characterized by extensive skin involvement, severe hepatic and renal injury and pulmonary manifestations, and features suggestive of macrophage activation syndrome. The case also illustrates the challenges of managing severe DRESS in the pediatric population.

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Case Presentation

A 15-year-old girl was admitted to the hospital for suspected measles encephalitis. Her medical history was notable for autism spectrum disorder and epilepsy diagnosed at five years of age. She had initially been treated with sodium valproate and clobazam. Because of an increase in seizure frequency, treatment was subsequently modified to clobazam and carbamazepine, with lamotrigine being the last treatment added approximately two months before the onset of the symptoms described below.

The patient was initially stabilized regarding her symptoms related to measles. On day 11 of hospitalization, the patient developed a generalized erythematous, maculopapular, and desquamative eruption involving more than 50% of the body surface area, facial and peripheral edema, as well as oral mucosal lesions. Vesiculobullous lesions were also noted on the neck, elbow, and thigh (Figures 1, 2). She was febrile and had a markedly altered general condition with the onset of drowsiness. Physical examination found hepatomegaly but no lymphadenopathy.



FIGURE 1: Upper limb erosive and erythematous plaques with bullous lesions in DRESS syndrome

DRESS: Drug reaction with eosinophilia and systemic symptoms



FIGURE 2: Necrotic eschar with surrounding violaceous discoloration and epidermal detachment in the gluteal region in the patient with DRESS syndrome

DRESS: Drug reaction with eosinophilia and systemic symptoms

Laboratory investigations revealed marked increased leukocytosis of 19,500 cells/mm³ (reference range: 4500-11000 cells/mm³) with a moderate increase in eosinophilia and monocyte count. No atypical lymphocytes were identified on the peripheral blood smear. The patient had acute kidney injury, with very high blood urea and serum creatinine values, associated with hypernatremia. Liver tests demonstrated severe hepatocellular injury, with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels 18 and 10 times the upper limit of normal, respectively. Gamma-glutamyl transferase was five times the upper limit of normal, and alkaline phosphatase was 1.5 times the upper limit of normal. Serum albumin was decreased, while the prothrombin time was markedly reduced to 8%, indicating severe hepatic dysfunction. A pronounced inflammatory response was also observed, with increased ferritin and triglyceride values as well as C-reactive protein, which reached a value of 68.2 mg/L, and lactate dehydrogenase at 1431 U/L. Fibrinogen was reduced. Taken together, these findings raised concern for macrophage activation syndrome in the context of severe systemic inflammation.

The infectious workup was negative for Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, and hepatitis A, B, and C viruses. HHV-6 testing was not performed. A subsequent chest radiograph demonstrated a pulmonary infiltrate (Figure 3).

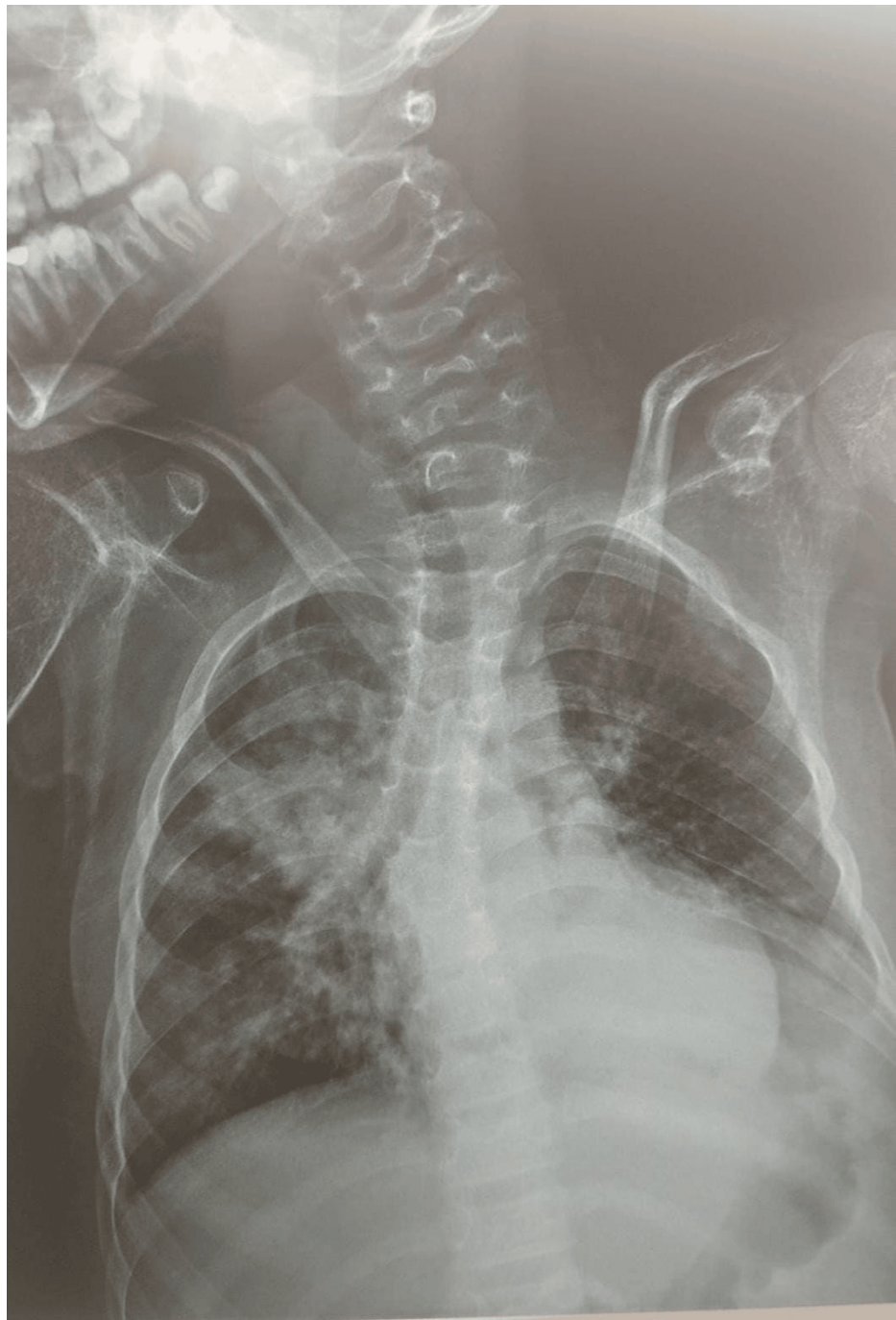


FIGURE 3: DRESS syndrome complicated by respiratory involvement and pulmonary infiltrates on chest radiography

DRESS: Drug reaction with eosinophilia and systemic symptoms

Given the delayed onset of symptoms after exposure to high-risk antiepileptic drugs, the extensive cutaneous eruption, facial edema, eosinophilia, and severe multiorgan involvement, a diagnosis of DRESS syndrome was made using the RegiSCAR criteria. Carbamazepine and lamotrigine were immediately discontinued and replaced with levetiracetam. The adverse drug reaction was reported to the pharmacovigilance service. Systemic corticosteroid therapy was initiated at a dose of 1 mg/kg/day. Supportive management included intravenous hydration, correction of hypernatremia, vitamin K administration, and albumin infusion for three days.

Initially, the patient demonstrated partial clinical and laboratory improvement (Table 1). The patient was afebrile with no appearance of new skin lesions. Renal function improved, with urea and creatinine decreasing, while serum sodium levels normalized. Hepatic parameters also improved, with

AST decreasing to six times the upper limit of normal and ALT to two times the upper limit of normal. Hepatic synthetic function improved, with the prothrombin time increasing to 70% and serum albumin to 35.3 g/L. Lactate dehydrogenase and triglyceride levels decreased, although ferritin remained elevated. The eosinophil count normalized to 300 cells/mm³.

Laboratory marker	Normal values	Initial values	Control values
Eosinophil	<500 cells/mm³	1,000 cells/mm³	300 cells/ mm³
Monocyte	200-800 cells/mm³	1600 cells/mm³	(-)
AST	10-40 UI/L	*18 upper normal	*6 upper normal
ALT	7-40 UI/L	*10 upper normal	* 2 upper normal
Albumin	35–50 g/L	24.6 g/L	35.3 g/L
Prothrombin time	70%-100%	8%	70%
Urea	0,15- 0,45 g/L	1.60 g/L	0.21 g/L
Creatinine	2–8 mg/L	22 mg/L	5.4 mg/L
Natremia	135-145 mEq/L	150 mEq/L	139 mEq/L
ferritin	20-150 ng/mL	504.52 ng/mL	(-)
Triglycerides	< 0,90 g/L	4.47 g/L	(-)
Fibrinogen	2–5 g/L	1.32 g/L	(-)

TABLE 1: Laboratory marker evolution in the reported patient

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; *: multiplied

After a period of apyrexia and stabilization of the cutaneous lesions, the patient developed recurrent high-grade fever reaching 40°C that was refractory to antipyretic therapy. This was accompanied by worsening respiratory distress, including tachypnea and increased work of breathing. Laboratory testing revealed further leukocytosis, reaching 23,200 cells/mm³, with marked neutrophilia (20,300 cells/mm³; reference range: 1700- 7500 cells/mm³) and worsening of the radiological findings.

The patient's respiratory condition progressively deteriorated, and she ultimately died from severe respiratory failure.

Discussion

DRESS syndrome is a delayed drug-induced hypersensitivity reaction with a characteristic latency period that generally ranges from two to eight weeks after initiation of the culprit medication [1,2]. This delayed presentation can complicate its recognition, particularly when several medications have been initiated or modified within the preceding weeks. The syndrome is characterized by a combination of fever, diffuse skin eruption, facial edema, lymphadenopathy, hematologic abnormalities, and internal organ involvement [1,2].

The pathophysiology of DRESS is complex and involves drug-specific T-cell-mediated immune responses, genetic susceptibility, and, in some patients, reactivation of latent viruses [2-4]. Reactivation of HHV-6 has been particularly associated with DRESS, although EBV, CMV, and HHV-7 reactivation may also occur [3]. In the present case, HHV-6 testing was not performed; therefore, the possible contribution of viral reactivation cannot be established. Drug exposure is recognized as the most common identifiable trigger of DRESS syndrome. A wide range of medications has been implicated as important triggers including aromatic anticonvulsants such as carbamazepine, phenytoin, phenobarbital, and lamotrigine, as well as allopurinol, antibiotics, antiretroviral agents, and several nonsteroidal anti-inflammatory drugs [1,2,6]. Several mechanisms have been proposed, including abnormalities in drug metabolism, immune dysregulation, and genetic susceptibility [2,4]. Inherited variations in drug-metabolizing or detoxification pathways may in particular contribute to the accumulation of reactive metabolites and subsequent immune activation [4]. In addition, specific human leukocyte antigen (HLA) polymorphisms have been associated with susceptibility to severe drug hypersensitivity reactions involving certain medications, including carbamazepine and allopurinol [4,9]. Among anticonvulsants, aromatic agents such as phenytoin, carbamazepine, lamotrigine, and phenobarbital have frequently been associated with severe cutaneous adverse reactions, including DRESS [1,2]. In our patient, lamotrigine had been introduced approximately seven to eight weeks before the

onset of the eruption, which is compatible with the typical latency period. Because carbamazepine was also being administered, attribution to a single culprit drug is difficult. Both drugs were therefore appropriately discontinued.

The RegiSCAR score is useful for standardizing the diagnosis of DRESS. The system incorporates fever, lymphadenopathy, atypical lymphocytes, eosinophilia, extent and characteristics of the skin eruption, biopsy findings, internal organ involvement, clinical resolution, and exclusion of alternative diagnoses [7,8]. A score below 2 is generally considered inconsistent with DRESS, 2-3 indicates a possible case, 4-5 a probable case, and 6 or higher a definite case [7,8].

Clinically, our patient exhibited several characteristic manifestations of DRESS. These included high-grade fever, an extensive maculopapular and desquamative eruption involving around 50% of the body surface area, facial and peripheral edema, vesicubullous lesions, and oral mucosal involvement. Eosinophilia was present, although the absolute eosinophil count of 1,000 cells/mm³ represented moderate rather than severe eosinophilia. It is, though, important to note that eosinophilia is not invariably present at disease onset and may evolve during the clinical course [2,6]. The visceral involvement in this patient was particularly severe. Hepatic involvement is the most frequent systemic manifestation of DRESS and ranges from asymptomatic elevation of transaminases to severe hepatitis and acute liver failure [1,2,6]. In our patient, AST and ALT were markedly elevated and were accompanied by severe impairment of hepatic synthetic function, reflected by a prothrombin time of only 8%. Renal involvement was also present, manifested by acute kidney injury. Pulmonary involvement subsequently became clinically prominent, while neurological manifestations were difficult to distinguish from the underlying suspected encephalitis. The coexistence of multiple organ abnormalities illustrates the potentially fulminant nature of severe DRESS [2,6]. The marked hyperferritinemia, hypertriglyceridemia, elevated lactate dehydrogenase, and hypofibrinogenemia raised the possibility of macrophage activation syndrome. Hematologic and inflammatory complications, including hemophagocytic or macrophage-activation phenomena, have been described in association with severe DRESS [2,10]. In the present patient, the extensive skin involvement, eosinophilia, multiple visceral organs affected, and exclusion of several alternative infectious diagnoses strongly supported DRESS with a score of 5 according to the RegiSCAR diagnostic scoring system [7,8].

Pediatric DRESS deserves particular attention as the available evaluations were historically extrapolated from adult populations [6]. A systematic review of 148 pediatric patients demonstrated that skin involvement was present in 97.9% of cases and that hepatic involvement occurred in approximately 84.5% [5]. Another systematic review of 354 pediatric patients found that antiepileptic drugs were the principal trigger group and that relapse was associated with features including fever, facial edema, lymphadenopathy, pharyngeal involvement, and visceral disease [11]. The recently published European Academy of Allergy and Clinical Immunology (EAACI) position paper specifically addresses the diagnosis and management of DRESS in children and proposes a severity-based pediatric algorithm [6]. These recommendations emphasize that children suspected of having DRESS should undergo an early assessment for severity and potential danger signs, with hospitalization and close clinical and laboratory monitoring recommended for suspected pediatric cases, particularly when systemic involvement is present. All suspected culprit medications should be discontinued promptly, together with potentially cross-reactive medications until an appropriate drug-allergy evaluation has been completed [6].

Supportive care includes careful skin care, emollients and dressings when necessary, nutritional support, management of fever, H1 antihistamines for severe pruritus, and correction of fluid and electrolyte disturbances [6]. The current pediatric EAACI position paper recommends prednisone or prednisolone at approximately 1-2 mg/kg/day, adjusted according to disease severity [6]. The duration of corticosteroid therapy is particularly important. Rapid tapering may be followed by disease flare or recurrence. The pediatric EAACI recommendations advise gradual tapering after clinical and laboratory resolution, generally over at least six weeks to three months, and potentially up to six months in severe Grade 3 disease [6]. If relapse occurs during tapering, the corticosteroid dose should generally be returned to the previously effective dose and subsequently reduced more slowly [6]. In severe or life-threatening DRESS, intravenous immunoglobulin (IVIG), cyclosporine, or other corticosteroid-sparing therapies may be considered in specialized settings. Evidence for these approaches in children remains limited [6,12,13]. The pediatric EAACI position paper suggests IVIG at 1-2 g/kg over three to five days in selected patients who do not respond adequately to systemic corticosteroids or who deteriorate clinically [6]. Treatment should therefore be individualized according to disease severity and organ involvement, ideally within a multidisciplinary pediatric setting.

Immediate withdrawal of the culprit medication remains the cornerstone of management. In our case, the initial biochemical improvement following drug withdrawal and corticosteroid therapy was encouraging but did not prevent subsequent deterioration. The recurrence of high-grade fever with respiratory failure demonstrates that clinical improvement of individual laboratory parameters does not necessarily indicate complete resolution of DRESS. The patient's fatal outcome may have resulted from severe pulmonary involvement, an evolving systemic inflammatory process, infection, or a combination of these mechanisms.

Long-term follow-up is also important in DRESS because delayed relapses and autoimmune reactions may occur after apparent clinical recovery [2,6,14]. Autoimmune thyroid disease is among the reported long-term

complications, and delayed endocrine abnormalities have been described in both pediatric and adult patients [14]. The introduction of new medications should therefore be undertaken cautiously because patients with DRESS may subsequently develop additional drug hypersensitivity reactions [6]. Finally, pharmacovigilance reporting is essential. Patients should receive clear documentation of the suspected culprit drug(s), and future exposure should be avoided. In patients with anticonvulsant-associated DRESS, the selection of alternative antiseizure therapy requires particular caution and should ideally involve pediatric neurology and allergy/immunology specialists [6].

Conclusions

DRESS syndrome is a rare but potentially fatal drug-induced hypersensitivity reaction that should be considered in any child or adolescent who develops fever and a widespread cutaneous eruption several weeks after exposure to a high-risk medication, particularly an aromatic antiepileptic drug.

The present case illustrates the potential for DRESS to produce severe multiorgan disease, including hepatic failure, acute kidney injury, pulmonary involvement, neurological manifestations, and marked systemic inflammation.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Achraf Cherrat

Acquisition, analysis, or interpretation of data: Achraf Cherrat

Drafting of the manuscript: Achraf Cherrat

Critical review of the manuscript for important intellectual content: Achraf Cherrat

Disclosures

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