Fever with pancytopenia in a patient with lamotrigin induced DRESS syndrome: a case-based review

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ABSTRACT

Background: Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a rare idiosyncratic and unpredictable drug reaction most commonly attributed to anticonvulsants, allopurinol, and antibiotics. Fever in combination with cutaneous manifestations and eosinophilia are the cardinal clinical findings, while organ involvement and very rarely pancytopenia can be present.

Case presentation: We describe a 26-year-old female patient with pancytopenia in the context of lamotrigine-induced DRESS and we summarize this as a potentially life-threatening hypersensitivity reaction.

Conclusion: DRESS should be suspected in patients presenting with fever, eosinophilia, skin involvement, and/or visceral organ involvement, who have started a new drug during the past 2 to 6 weeks, as early recognition of this syndrome with subsequent discontinuation of the offending drug could be lifesaving.

Keywords: DRESS; lamotrigine; hypersensitivity reaction; pancytopenia; glucocorticoids.

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Background

Drug rash with eosinophilia and systemic symptoms (DRESS) is an uncommon and severe multiorgan hypersensitivity drug reaction characterized by skin lesions in combination with organ involvement and eosinophilia. Its true incidence remains unclear although the estimated incidence seems to vary between 1 in 1,000 and 1 in 10,000 exposures. Reactivation of human herpesviruses (HHV), with HHV-6 being the most common cause, plays a significant role in the etiopathogenesis of the syndrome, affecting the overall prognosis [1,2]. The clinical manifestations can be potentially life-threatening and usually appear at least 2 weeks after exposure to the triggering factor. Up to 25% of the patients relapse usually within 5 months after the resolution, typically in cases treated with systemic glucocorticoids and usually due to rapid tapering. Long-term complications of the syndrome include the onset of autoimmune diseases, such as autoimmune hemolytic anemia, Graves, or Hashimoto disease. Drug withdrawal, supportive treatment, and monitoring are the hallmark of treatment, although in severe cases systemic corticosteroids are the treatment of choice [1-3]. Herein, we describe a 26-year-old patient with DRESS and pancytopenia attributed to lamotrigine, who responded successfully to oral prednisolone.

Case Presentation

A 26-year-old female patient presented to our hospital due to a high-grade fever with generalized itchy skin rash, which had started 10 days before. Her past medical history was remarkable for depression for which she received fluoxetine with the addition of lamotrigine 1 month before the onset of the symptoms. On physical examination, the patient was alert, oriented, and conscious and had fever in combination with a maculopapular rash predominantly located in the trunk and the extremities. Furthermore, cervical and inguinal lymphadenopathy together with splenomegaly was observed. Laboratory investigation immediately after admission, revealed pancytopenia and eosinophilia: white blood cells = 1.450 cells/mm^3; hemoglobin = 10 g/dl, platelets = 120.000 cells/mm^3 and eosinophils = 530 cells/mm^3, while inflammatory markers were within the normal range [C-Reactive-Protein (CRP) = 1 mg/dl and

Erythrocyte Sedimentation Rate (ESR) = 20 mm/hour]. In the context of the differential diagnosis, we performed serological tests for viruses [Epstein Barr Virus (EBV), Cytomegalovirus (CMV), Herpes Simple Virus (HSV), Varicella Zoster Virus (VZV), HHV-6, HHV-8, Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), and Parvovirus B19] and *Bartonella henselae* and *Bartonella Quintana*, which were normal. Renal and liver function tests and electrolytes were normal with a mild increase of Lactate Dehydrogenase (LDH) (360 IU/l). In addition, anemia laboratory markers (ferritin, B12, folic acid), tumor markers, and serologic investigations for autoimmune diseases were performed [Anti-nuclear Antibodies (ANA), anti-dsDNA, RF, C3, and C4] and were also negative, as well as blood and urine cultures. Cardiac electrocardiography and echocardiography didn't show any pathological findings, while cervical and abdominal ultrasonography confirmed lymphadenopathy and splenomegaly. Thus, we decided to perform a skin biopsy, which showed a small vessel leukocytoclastic vasculitis compatible with DRESS (Figure 1). Excluding all the other possible causes, our patient was diagnosed with DRESS, as defined by the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system. Lamotrigine was immediately discontinued, and the patient was administrated on oral prednisolone at the dose of 1 mg/kg/day for 2 weeks, which was tapered over a period of the next 4 weeks, leading into remission over a period of 10 days. One year after the first occurrence of her symptoms, the patient remains well.

Discussion

DRESS is an uncommon idiosyncratic T-cell mediated hypersensitivity reaction, most often affecting hospitalized patients, accounting for about 15% of all cutaneous adverse drug reactions. Most reports agree that there is no age or sexual preference, although a slight female dominance can be seen in some of them. In the vast majority, a clear drug triggering factor can be identified and the overall mortality is estimated to be approximately 10%.

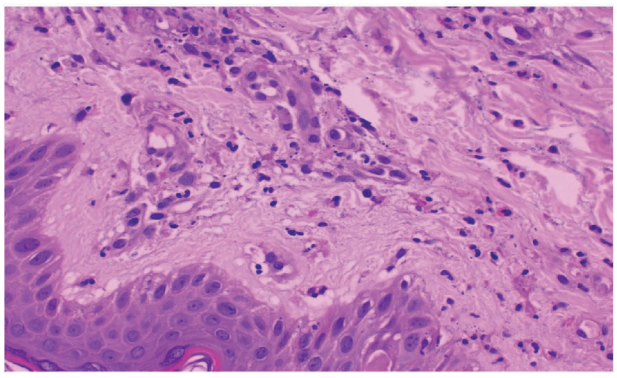

Figure 1. *Leukocytoclastic vasculitis: superficial and mild perivascular inflammatory pattern (H-E stain ×200).*

The most commonly implicated drugs are allopurinol, sulfonamides, antibiotics, antiepileptic and antituberculosis agents. Aromatic antiepileptic drugs, such as carbamazepine and lamotrigine are a typical causative factor in contrast to non-aromatic agents (valproic acid and topiramate) [1-3] (Table 1).

In up to 75% of the patients, reactivation of Herpesviridiae seems to be present, characteristically following the occurrence of the disease. Although the responsible mechanisms remain largely unclear, Herpesviridiae reactivation seems to affect negatively the overall prognosis, with HHV-6 and CMV being associated with poorer outcomes [4]. The pathogenesis of DRESS is not well understood. Genetic association of human leukocyte antigens [Human Leukocyte Antigen (HLA) system] and accumulation of drug metabolites due to deficiency of enzymes, which are responsible for detoxification, seem to contribute significantly to the pathogenesis of the syndrome.

DRESS usually develops 2 to 6 weeks after drug exposure and presents with a wide range of symptoms and signs. The most common manifestations are fever and rash in combination with lymphadenopathy, and hematological and liver function tests abnormalities. The urticarial

Table 1*. High and low risk etiologic agents of DRESS syndrome.*

HIGH-RISK AGENTS	LOW-RISK AGENTS
• Allopurinol	• NSAIDs
• Sulfonamides, Dapsone	• Omeprazole
• Vancomycin	• Captopril, Atenolol, Diltiazem
• Minocycline	• Gold Salts
• Aromatic anticonvulsants	• Olanzapine
	• Fluoxetine
1.Carbamazepine	• Imatinib
2.Phenytoin	• Sorafenib
3.Phenobarbital	
4.Lamotrigine	
• Isoniazid, Rifampicin	
• Pyrazinamide, Ethambutol	
• Nevirapine, Mexiletine	

Table 2*. Diagnostic criteria for DRESS by the RegiSCAR (the first three criteria are necessary for diagnosis, and the presence of three out of the other four criteria).*

1. Acute rash
2. Reaction suspected drug-related
3. Hospitalization
4. Fever > 38°C
5. Laboratory abnormalities (at least one of them) :
* Lymphocyte above or below normal
* Low platelet
* Eosinophilia
6. Involvement of > one internal organ
7. Enlarged lymph nodes > two sites

maculopapular eruption is the prominent cutaneous phenotype, while in other cases purpura, erythroderma, and skin target lesions can be present. It is noteworthy that in extremely rare cases, the cutaneous manifestations are absent, making the diagnosis even more difficult [3,4]. Eosinophilia is the most frequent hematological finding occurring in>50% of the patients and leukocytosis or lymphocytosis may coexist. In about 50% of the cases, atypical lymphocytes are present in the peripheral blood smear. On the contrary, pancytopenia is a much less common finding, associated with a poor prognosis, as it may lead to increased rates of admission to the intensive care unit or even death [4,5].

Visceral involvement is the major cause of mortality and morbidity and occurs in about 90% of the patients, while in some cases may precede the development of the skin rash. The liver is the most commonly affected organ, while cardiac, pulmonary, and kidney involvement may be seen. Transaminasemia, acute cholestasis, dyspnea, dry cough, proteinuria, and acute intestinal nephritis are the most prominent manifestations. In rare cases, patients develop symptoms of the central and peripheral nervous system, such as aseptic meningitis, Bell's palsy, and peripheral neuropathy, whereas hemophagocytic syndrome is considered an infrequent, but potentially life-threatening sequelae of the syndrome. Skin biopsy plays a crucial role in elucidating the diagnosis, while the RegiSCAR scoring system is the most widely used diagnostic tool [5] Table 2.

The differential diagnosis mainly includes Kawasaki syndrome, hypereosinophilic syndrome, lymphomas, acute cutaneous lupus erythematosus, and Stevens-Johnson syndrome/toxic epidermal necrolysis or acute generalized exanthematous pustulosis. In mild disease without organ involvement or only mild liver involvement, discontinuation of the causative medication and supportive/symptomatic treatment is the mainstay of treatment. However, patients with the severe disease with a single or multiple organ injury should receive systemic glucocorticoids, while cyclosporine and intravenous immunoglobulin are alternative options, especially in non-responding cases [4-7].

This was a rare case of lamotrigine-induced DRESS due to the concurrent pancytopenia, which resolved rapidly after drug discontinuation as well as corticosteroids treatment. As pancytopenia is considered a poor prognostic factor among patients with DRESS, it prompted the administration of corticosteroids, which resulted in quick and impressive response in this patient.

Conclusion

DRESS should be suspected in patients presenting with fever, eosinophilia, skin involvement, and/or visceral organ involvement, who have started a new drug during the past 2 to 6 weeks, as early recognition of this syndrome with subsequent discontinuation of the offending drug could be lifesaving.

What is new?

Lamotrigine-induced DRESS syndrome has been well described, but the presence of pancytopenia apart from eosinophilia indicates a poor prognosis. Therefore, the use of glucocorticoids according to the RegiSCAR scoring system seems beneficial in such cases. Herein, the authors present a 26-year-old female patient with lamotrigine-induced DRESS syndrome and pancytopenia, the presence of which mandated the use of glucocorticoids.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written and informed consent was taken from the patient to publish this case report.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient details**	26-year-old female patient
2	**Symptoms**	Fever, Rash and Pancytopenia
3	**Final diagnosis**	DRESS Syndrome
4	**Medication**	Corticosteroids
5	**Clinical procedures**	Skin Biopsy and administration of glucocorticoids
6	**Clinical specialty**	Internal Medicine