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Darrell Downs
Department of Internal Medicine, University of Illinois College of Medicine, Peoria, IL1,
darrelljdowns@gmail.com

Keerthana Sivakolundu
Department of Internal Medicine, University of Illinois College of Medicine, Peoria, IL1

Nica Lim
Department of Internal Medicine, University of Illinois College of Medicine, Peoria, IL1

Manasa Kandula
Department of Internal Medicine, University of Illinois College of Medicine, Peoria, IL1

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CASE REPORT

Valacyclovir as Etiology for Drug Reaction with Eosinophilia and Systemic Symptoms: A Case Report

Darrell Downs*, Keerthana Sivakolundu, Nica Lim, Manasa Kandula

Department of Internal Medicine, University of Illinois College of Medicine, Peoria, IL, USA

Abstract

Background: **Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially life-threatening condition associated with variable clinical presentations including rash, fevers, eosinophilia, and visceral organ involvement. It is a hypersensitivity reaction, and most cases have an identifiable inciting factor of drug exposure.**

Case presentation: **We present an interesting case of DRESS syndrome in a 97-year-old patient after she was treated with valacyclovir for herpes zoster. Her presentation included an exanthematous rash, acute kidney injury and progression to development of mildly elevated liver enzymes. Skin biopsy was consistent with DRESS. Patient initially responded to steroids but had a relapse during steroid taper. She eventually responded well to a slow prolonged steroid taper and had complete resolution of organ dysfunction and skin manifestations.**

Conclusion: **Valacyclovir is a rare but important cause of DRESS. A thorough history of the illness timeline and a high index of clinical suspicion is required for the prompt diagnosis and treatment of the condition. Apart from withdrawal of the offending agent, a slow prolonged taper of steroids is the current recommended treatment as rapid reduction of steroid dosage can lead to a relapse of cutaneous and systemic symptoms.**

Keywords: Drug reaction with eosinophilia and systemic symptoms, DRESS syndrome, Drug reaction, Valacyclovir, Herpes zoster, Human herpesvirus 3

1. Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially life-threatening adverse drug reaction with variable clinical manifestations and an unpredictable course. In general, DRESS syndrome includes severe skin eruption with an extensive rash, fevers, eosinophilia, and lymphocytosis with evidence of visceral organ involvement.[1-4] Although the exact pathophysiology remains unclear, DRESS is considered a hypersensitivity reaction mediated by T-cells. Most cases of DRESS have a recognizable precipitating factor including drugs such as antibiotics, anticonvulsants, and allopurinol.[4] Furthermore, reactivation of DNA virus from the Herpesviridae family is a well-established phenomenon. Herein, we present an interesting case of DRESS syndrome presenting with acute onset of a severe exanthematous rash after 2 weeks of outpatient therapy with valacyclovir for herpes zoster.

2. Case presentation

A 97-year-old female with a past medical history of chronic kidney disease, atrial fibrillation, hypertension, hypothyroidism, heart failure with reduced ejection fraction and sulfa allergy, was admitted with a severe exanthematous drug rash. Two weeks prior to presentation, the patient was seen by Ophthalmology for a rash above her left eye and associated left eye pain. She was diagnosed with herpes zoster and started on a 7-day course of oral valacyclovir and prednisone eye drops. Patient returned a few days after completing her course of valacyclovir for follow-up. At this time, she was restarted on valacyclovir for another 7-day course.

Three days later, she developed a new urticarial rash on her chest and back. She self-treated herself at home with cetirizine with no improvement. Over the next 2–3 days, her rash worsened and spread to her face, neck, and bilateral upper and lower extremities. On presentation, she was afebrile and

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* Corresponding author.
E-mail address: DarrellJDowns@gmail.com (D. Downs).

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hypotensive (Blood Pressure 89/42 mmHg), and tachypneic. On physical examination, she had a diffuse exanthematous rash on her face, neck, trunk and all the extremities without any evidence of mucosal involvement, bullae, vesicles or sloughing of the skin (Fig. 1A–D). Initial laboratory findings were significant for leukocytosis (26.44 × 103/mcL) with an elevated absolute eosinophil count of 0.98 × 103/mcL, mildly elevated C-reactive protein at 0.78 mg/dL and elevated troponin at 56 ng/L. Metabolic panel showed an elevated creatinine of 1.98 mg/dL, increased from her baseline of 1.5 mg/dL, and sodium of 130 mmol/L. At the time of admission, liver function tests were unremarkable. Our differential diagnosis at this time included a drug-induced skin rash/eruption vs DRESS with a low suspicion for Steven Johnson Syndrome or Toxic Epidermal Necrolysis given lack of mucosal involvement or skin sloughing.

A thorough review of her medication list was done which showed she was taking carvedilol, furosemide, levothyroxine, losartan, pravastatin, warfarin, and hydrocodone-acetaminophen for many years now, with recent addition of valacyclovir within the last 2 weeks. Valacyclovir was discontinued. The patient was started on intravenous fluids and a tapering dose of intravenous steroids (methylprednisolone 125 mg followed by 62.5 mg and 32 mg in the next two 12-h intervals). One day after admission, her rash and renal function improved, and she was transitioned to oral prednisone (prednisone 40 mg daily) due to clinical improvement. Blood cultures were negative, EBV IgM was negative, and IgG was positive consistent with past EBV infection; CMV IgG was >8.0 and IgM was 0.2, also consistent with past exposure. Skin biopsy was performed which noted *"Vacuolar interface dermatitis with epidermal spongiosis and mixed acute and chronic dermal inflammation including scattered eosinophils"* which is consistent with DRESS (Fig. 1E and F). After steroid dosage was decreased, rash clinically worsened, and labs showed worsening eosinophilia (2.18 × 103/mcL). She also developed a mild transaminitis AST 51 U/L, ALT 79 U/L. After consulting with our Dermatology team, we escalated her steroid dose. She was started back on intravenous methylprednisolone at 40 mg twice daily. The rash continued to improve with normalization of renal function, liver function, and absolute eosinophilia. Patient was eventually discharged on oral prednisone 60 mg daily followed by a prolonged taper over 8–12 weeks, and topical triamcinolone cream. Patient continued to do well at outpatient follow-up after completion of treatment with steroids.

3. Discussion

DRESS, previously known as drug-induced hypersensitivity syndrome (DIHS), is a potentially life-threatening adverse drug reaction with a wide range of clinical manifestations which typically appear 2–8 weeks after the initiation of the causative drug.[1] Its incidence is estimated to be between 1 in 1000 to 1 in 10,000 exposures.[2-5] Common features include

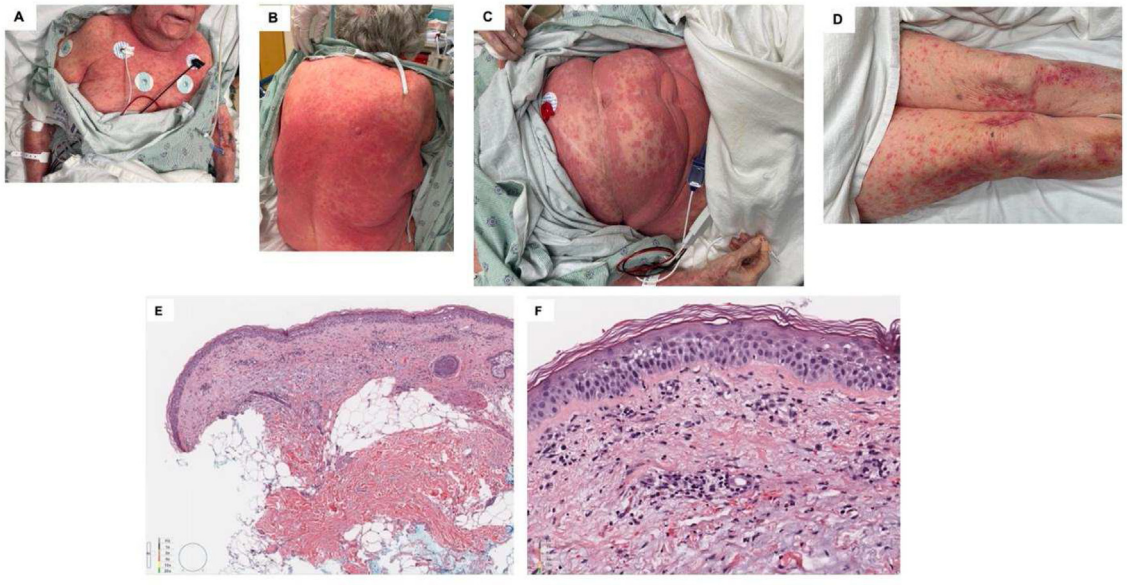

Fig. 1. A–D noting diffuse exanthematous rash. 1E. Skin biopsy at 4x magnification. 1F. Skin biopsy at 20x magnification. Skin punch biopsy with mild spongiosis as well as vacuolar changes. The dermis contains solar elastosis along with perivascular and interstitial inflammatory infiltrate composed of eosinophils, neutrophils, lymphocytes and histiocytes.

fever, rash, lymphadenopathy, leukocytosis with eosinophilia, and abnormal liver function tests.[1] The rash usually begins as an urticarial erythematous macule that starts on the face and upper trunk, and expands caudally.[2] In some patients, vesicles, bullae, pustules, purpura, target lesions, facial edema, cheilitis, and erythroderma have also been reported.[2] Visceral involvement can occur in the form of hepatitis, pneumonitis, myocarditis, pericarditis, nephritis, and colitis which are the major cause of morbidity and mortality in this syndrome.[1] A noteworthy feature of DRESS is the possible persistence or aggravation of symptoms despite discontinuation of the triggering agent.[3]

The most frequently reported culprit drugs include carbamazepine, phenobarbital, allopurinol, and sulfasalazine, but over 50 drugs have been associated with DRESS (Table 1).[3,4,6-13] Our patient developed diffuse urticarial rash approximately 2 weeks after starting valacyclovir for herpes zoster. The rash started as an urticarial macule on the chest and worsened after valacyclovir was restarted. A thorough medication review and the clinical course of our patient suggested that valacyclovir was likely the causative drug. DRESS after valacyclovir is a poorly described phenomenon in the literature, with only three cases described so far in a single case series.[14] In each of these cases, drugs better known to be associated with DRESS such as cotrimoxazole, bendamustine, and penicillin V were initially suspected as the causative drugs.[14] However, the clinical course showing a lack of improvement after withdrawing the other culprit drugs or worsening of the symptoms after restarting valacyclovir highly suggested the causality of valacyclovir.[14] Positive results of patch tests for valacyclovir performed later also provided further evidence.[14]

The diagnosis of DRESS syndrome is mainly clinical, and one must consider the latency period, a broad range of clinical symptoms, and exclusion of similar non-drug-related conditions.[15] Three different sets of criteria that are used to diagnose DRESS syndrome are shown in Table 2.[15] Our patient satisfied Bocquet's and Regi-SCAR criteria but not the Japanese group criteria. Kim DH and colleagues compared the diagnostic criteria for DRESS and stated that Bocquet's criteria and Regi-SCAR criteria should be complementary for the diagnosis of DRESS in suspected patients.[15] The Japanese DIHS criteria may be too strict to diagnose DRESS syndrome and represent a severe subgroup of DRESS.[15] The diagnosis of Japanese DIHS requires evidence for the reactivation of HHV-6,9 which is not included in Regi-SCAR or Bocquet's criteria.[15]

The exact pathophysiology of DRESS has not been completely elucidated but it has been suggested that defects in the detoxification of certain drugs' active metabolites in predisposed patients with genetic or acquired variations, may cause a hypersensitivity reaction mediated by T cells.[1] Our patient had a known sulfa drug allergy, which could have put her at an increased risk for a hypersensitivity reaction. We also cannot neglect the possibility of DRESS after recent herpes zoster reactivation. Several herpesviruses including Epstein–Barr virus, HHV-6, HHV-7, and cytomegalovirus may play a critical role in the pathogenesis of DRESS.[16] Two scenarios have been suggested, one being an immune response against the drug which causes secondary viral reactivation, and the other one being early viral reactivation which is responsible for most of the manifestations of DRESS syndrome.[17] Our patient had herpes zoster infection before the diagnosis of DRESS syndrome. Although the association of

Table 1. Drugs frequently causing DRESS.[3,4,6-13]

More Common Drugs

- Allopurinol
- Antiepileptic agents
  - Carbamazepine
  - Phenytoin
  - Lamotrigine
  - Oxcarbazepine
  - Phenobarbital
- Antibiotics with Sulfonamides
  - Sulfasalazine
  - Dapsone
  - Trimethoprim-sulfamethoxazole
  - Vancomycin
- Anti-tuberculosis agents
  - Rifampicin
  - Isoniazid
  - Pyrazinamide
  - Ethambutol

Less Common Drugs

- Antibiotics – beta-lactams
- Anti-psychotic/Anti-depressant
  - Olanzapine
  - Fluoxetine
- Non-steroidal anti-inflammtory (NSAIDs)
  - Ibuprofen
  - Celecoxib
  - Diclofenac
- Anti-tumor
  - Sorafenib
  - Imatinib
  - Vemurafenib
- Others
  - Omeprazole
  - Raltegravir

Table 2. Diagnostic criteria for DRESS.[15]

Regi-SCAR criteria Require at least 3 of the following 7 characteristics	Bocquet's criteria Require the following 3 features	Japanese group Require all the 7 features
Skin eruption	Skin eruption	Maculopapular rash developing >3 weeks after starting a limited number of drugs
Fever (>38 °C)	Blood eosinophilia (>1.5 × 10^3/μL) or the presence of atypical lymphocytes	Prolonged clinical symptoms 2 weeks after discontinuing the causative drug
Lymphadenopathy at least 2 sites	Internal organ involvement, including lymphadenopathies (>2 cm in diameter), hepatitis (liver transaminases values > twice the upper normal limit), interstitial nephritis, and interstitial pneumonia or carditis	Fever (>38 °C)
Involvement of at least 1 internal organ		Alanine aminotransferase [ALT] >100 U/L) or involvement of other organs
Lymphocytosis (>4 × 10^3/μL) or lymphocytopenia (<1.5 × 10^3/μL)		Leukocytosis (>11 × 10^3/μL), atypical lymphocytosis (>5%), or eosinophilia (>1.5 × 10^3/μL)
Blood eosinophilia (>10% or 700/μL)		Lymphadenopathy
Thrombocytopenia (<120 × 10^3/μL)		Human herpesvirus (HHV)-6 reactivation

HHV-6 has been extensively studied in the literature, there are some cases of association with varicella-zoster virus as well.[18] Thus, the patient's advanced age and comorbidities may have led to an immunocompromised state and subsequent reactivation of herpes zoster, which may have played a role in the development of DRESS.

There are no established guidelines to treat patients with suspected DRESS syndrome. The most important measure is the immediate withdrawal of the suspected drug, and supportive treatment to hemodynamically stabilize the patient.[18,19] Another key point to note is that the patient should not be given any empiric antibiotics or anti-inflammatory drugs during the acute stages of DRESS syndrome.[4] This can exacerbate the clinical condition due to unexplained cross-reactivity between drugs. Systemic corticosteroid therapy with a minimum dose of 1.0 mg/kg/day of prednisolone or equivalent with a gradual taper over 3–6 months is currently the most widely accepted and used treatment.[19] Rapid reduction in corticosteroid or accidental withdrawal has been reported to cause significant cutaneous and systemic symptoms which was the case in our patient.[4,20] In patients who fail to show improvement with oral steroids, pulsed methylprednisolone 30 mg/kg can be given intravenously for 3 days.[19] Other potential therapies include intravenous immunoglobulin (IVIG), plasmapheresis, and immunosuppressive drugs, such as cyclophosphamide, cyclosporine, and interferons, muromonab-CD3, mycophenolate mofetil, and rituximab.[19]

Patients with DRESS syndrome can also develop manifestations of autoimmunity such as thyroiditis, adrenal insufficiency, diabetes insipidus, connective tissue disease, or a reaction resembling graft-versus-host disease.[21] The death rate in DRESS syndrome is about 10% and is mostly due to liver failure.[22]

4. Conclusion

Valacyclovir is a possible cause of DRESS, which may be neglected due to its weak notoriety. It is important to include valacyclovir in the drugs that cause DRESS, because it helps to promptly identify patients who develop DRESS syndrome on valacyclovir. Herpes zoster infection could also be a possible trigger of DRESS syndrome, but it needs further research.

Prompt withdrawal of the offending agent along with systemic corticosteroids is the mainstay in the treatment of DRESS. Relapses are more common with rapid tapering or withdrawal of steroids. Therefore, it is important to continue steroids until the clinical and laboratory manifestations completely resolve and then taper them gradually.

5. Conflict of interest

There is no conflict of interest..

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