CASE REPORT

Drug rash with eosinophilia and systemic symptoms (DRESS) caused by phenytoin

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SUMMARY

Drug rash with eosinophilia and systemic symptoms (DRESS) is a rare but potentially life-threatening condition with high mortality. Diagnosis is challenging due to variable clinical presentation and a protracted latency period following initiation of the offending drug. DRESS is a complex interplay that starts by introduction of the offending drug, reactivation of viruses and activation of the immune system. Herpes virus reactivation is considered a diagnostic marker and indicator of illness severity. Prompt recognition and the removal of offending agent remain the key to successful treatment. In cases of severe organ involvement, corticosteroids, immunoglobulins, antiviral and specialist consultation may be helpful. Here we present a case of a 36-year-old African-American male who presented with symptoms mimicking sepsis with an associated skin eruption that was diagnosed as DRESS.

BACKGROUND

Drug rash with eosinophilia and systemic symptoms (DRESS) is a rare severe drug reaction with estimated mortality of 10%–20%.^{1–3} The exact prevalence of this syndrome is unknown. However, the prevalence of cutaneous drug reactions in a hospital setting is estimated at 3.6/1000, while the incidence of DRESS is around 1/1000 to 10 000.¹ Common drug groups implicated in DRESS include anticonvulsants, anti-inflammatory agents, antidepressants, sulfa drugs, ACE inhibitors, antibiotics and beta-blockers, although certain other individual drugs are also rarely implicated.^{4,5} Diagnosis of DRESS is exigent and challenging because of a wide differential, given the diversity of skin reactions, multitude of causative drugs, possibility of internal organ involvement and lack of stringent and unified diagnostic criteria. This syndrome usually presents 2–6 weeks after the start of an offending medication. Common signs and symptoms include skin eruption, fever, lymphadenopathy, haematological abnormalities and internal organ involvement. The mainstay of treatment is usually supportive along with prompt discontinuation of the responsible agent. The case here presented is that of a 36-year-old African-American prison inmate who was diagnosed with DRESS secondary to use of phenytoin.

CASE PRESENTATION

A 36-year-old African-American prison inmate with a medical history of asthma, bipolar disorder and

seizure disorder since childhood presented to the emergency department with 5-day history of sore throat, high-grade fever and difficulty swallowing with worsening facial swelling. The patient was on divalproex sodium for many years. However, levetiracetam was added recently after the patient fell and hit his head on the floor sustaining a seizure. He then suffered another seizure episode few weeks later. Both these episodes of seizures were witnessed by the staff. Given recurrence of seizures while being on levetiracetam, he was switched to phenytoin about 6–8 weeks prior to presentation to hospital. About 7 days prior to presentation, he was not feeling well and reported throat pain that made it difficult to swallow. Over the next 2 days, he developed facial and neck swelling along with eruption of an erythematous pruritic skin rash. In the emergency department, his review of symptoms was positive for fever, chills, arthralgias, sore throat, decreased per oral intake and facial and neck swelling. Physical exam recorded an initial blood pressure of 90/59 mm Hg, temperature of 39.1°C and an oral cavity exam essentially negative except erythematous areas on hard palate. Cervical and submandibular lymph nodes were enlarged. An erythematous, confluent, slightly warm to morbilliform rash covered the upper chest, upper back and both forearms, extending to the dorsal hands but sparing the palms and soles (figure 1). His home medications included benztropine mesylate oral 1 mg twice daily, hydrocortisone 1% topical as needed, mometasone furoate 200 mcg/5 mcg as needed twice daily, hydroxyzine 75 mg as needed nightly, acetaminophen with codeine 300 mg/30 as needed every 6 hours, loratadine 10 mg daily, ranitidine 150 mg twice daily, divalproex 500 mg twice daily, ziprasidone 60 mg twice daily, silver sulfadiazine 1% topically, levalbuterol inhalation 45 mcg daily as needed, benadryl 50 mg as needed and phenytoin 300 mg daily. He used recreational cannabis occasionally but denied tobacco or ethanol use.

INVESTIGATIONS

See table 1 for laboratory investigations.

TREATMENT

Initially, the patient received intravenous ceftriaxone since the clinical presentation mimicked sepsis given the presence of fever, leucocytosis and hypotension. Soon it was realised that the patient did not have lactic acidemia or signs of

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Figure 1 Morbilliform rash on left forearm.

compromised tissue perfusion. Given high eosinophilia (19.6%), skin eruption, lymphadenopathy, acute liver dysfunction and the knowledge of phenytoin use (6–8 weeks prior to presentation), a diagnosis of DRESS was made. Phenytoin was stopped. The patient empirically started on intravenous methylprednisolone due to severe facial and neck swelling as well as presence of liver dysfunction. A left forearm punch biopsy of skin obtained during hospitalisation displayed modest interface dermatitis without spongiosis or parakeratosis (figure 2). A perivascular and somewhat interstitial infiltrate of mononuclear cells were accompanied by neutrophils and eosinophils. Swollen endothelial cells and some extravasated red cells connoted vascular injury. Lymphatics were dilated. Inflammatory cells infiltrated follicular epithelium (figure 2A–C). The patient improved on intravenous methylprednisolone after discontinuation of phenytoin. His skin rash gradually improved with application of topical clobetasol.

OUTCOME AND FOLLOW-UP

At 1 week, the patient was doing well with steadily improving transaminases. Epstein-Barr virus (EBV) and human herpes virus 6 (HHV-6) titres were obtained at 2 weeks following the start of the illness. The plan was to repeat the sequential testing; however, these tests could not be done due to loss of follow-up as the patient was moved to another penitentiary.

DISCUSSION

Although several drug groups have been associated with DRESS, anticonvulsants are among the most commonly reported culprits. Unfortunately, anticonvulsants have been found to have long latency period of 1 week to 3 months making it extremely difficult to diagnose DRESS.^{6–7} Aromatic anticonvulsants such as phenytoin, carbamazepine, lamotrigine and so on are among the most commonly reported anticonvulsants associated with DRESS.⁸ Phenytoin was found to be the most common aromatic culprit for DRESS based on a retrospective study by Akarin *et al*, who screened more than half million admissions over a period of 11 years to assess the clinical course and causative drugs for DRESS.⁹ It remains unclear why phenytoin was more common

Table 1 Laboratory investigations

Investigation	Results
Complete blood count	White cell count: $15.8 \times 10^3/\mu\text{L}$ (neutrophils 42.2%, lymphocytes 28.1%, eosinophils 19.6%, monocytes 7.9%) Hb: 12.6 g/dL Platelets: $251 \times 10^3/\mu\text{L}$
Metabolic panel	Sodium 127 mmol/L, anion gap of 13, glucose 125 mg/dL otherwise unremarkable
Liver function and iron panel	Total bilirubin of 4.1 mg/dL: direct 2.0 mg/dL Alk P: 471 IU/L ALT: 434 IU/L AST: 310 IU/L Total protein: 6.4 g/dL
Coagulation studies	PT: 17.7 s INR: 1.5
Inflammatory markers	ESR: 23 mm/hour CRP: 8.80 mg/dL
Immunology	Hepatitis panel: negative HIV: negative ANA: negative HHV-6 antibody IgG: 1.40 (high) HHV-6 antibody IgM: <1.20 EBV D early antigen: 14.4 units/mL (high) EBV capsid antigen-IgG: 456.0 units/mL (high) EBV nuclear antigen: 360.0 units/mL (high)
Toxicology	Ethanol: negative Acetaminophen: negative Salicylate: negative Phenytoin: 6.5 mcg/mL, obtained next day Urine toxicology: negative
Urine analysis	Urine analysis: negative except proteinuria
Cultures	Blood, throat, methicillin-resistant <i>Staphylococcus aureus</i> : negative Group A streptococcus culture: negative Urine culture: negative
Radiology	Chest X-ray: negative Abdomen ultrasound: Mildly prominent bile duct at 6 mm otherwise unremarkable ultrasound. CT soft tissue neck with contrast: diffuse oedema throughout the neck and supraclavicular region with multiple small cervical chains, submental, submandibular supraclavicular lymph nodes, the largest being 13 mm.
Miscellaneous tests	Lactic acid: normal; ASO titre: normal

Alk P, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; ASO, antistreptolysin A titre; AST, aspartate aminotransferase; CRP, C reactive protein; EBV, Epstein-Barr virus; ESR, sedimentation rate; Hb, haemoglobin; HHV, human herpes virus; INR, international normalized ratio; PT, prothrombin time.

than other aromatics, as most of these drugs are chemically similar. This could just be random chance. The role of human leucocyte antigen (HLA) loci has been studied to see if any particular HLA type is more closely associated with cutaneous drug eruptions.^{10–11} Based on limited ethnic data, HLA-A*24:02 type was identified as shared risk factor among different types of anticonvulsants.¹¹ Furthermore, typing for HLA-B has been proposed in certain populations before initiating treatment with carbamazepine or phenytoin.¹⁰ Additional studies would be needed to definitely assess the risk factors and prevalence of DRESS among various anticonvulsants.

Drug-induced hypersensitivity with skin eruption was first reported in 1950 by Chaiken *et al* in a patient taking phenytoin. However, it was not until 1996 that Bocquet *et al* first introduced the term DRESS.^{2–12} According to a review of 172 cases of DRESS, it is more common in adults than children and has no

Figure 2 (A) A few inflammatory cells aggregate along the epidermal basement membrane of an epidermis without spongiosis or altered stratum corneum. Beneath is modest perivascular dermatitis with some interstitial extension ($\times 200$). (B) The eosinophils and neutrophils marginate in dermal vessels with swollen endothelial cells bordered by lymphocytes, histiocytes and extravasated red blood cells ($\times 400$). (C) Neutrophils join lymphocytes in exocytosis into follicular epithelium ($\times 200$).

gender predilection.¹³ Various mechanisms have been implicated in its pathogenesis. In cases of anticonvulsants, at least three distinct mechanisms have been described. These include either a deficiency or abnormality of the enzyme epoxide hydroxylase or glutathione transferase, reactivation of latent herpes virus and genetic predisposition to various HLA genes. Aromatic anticonvulsants are generally metabolised by the cytochrome P450 system into toxic intermediate arene oxide radicals that are in turn detoxified by these enzymes into non-toxic metabolites. Due to the deficiency of these enzymes in genetically predisposed individuals, impaired hydroxylation of aromatic amines can lead to tissue damage.^{14 15} Recent studies have suggested a

close relationship between HHV-6 as well as other herpes viruses such as EBV, cytomegalovirus and HHV-7.^{16 17} The evidence is much stronger for HHV-6, which is now being considered a diagnostic marker and has been linked to the severity of illness.¹⁸ Diagnosis of DRESS is challenging due to lack of stringent diagnostic criteria and inconsistent clinical features in various patient populations. The pertinent case however meets the majority of available diagnostic criteria that include that of the Japanese Study Group of Severe Cutaneous Adverse Reactions to drugs (SCAR-J), European group RegiSCAR and the early reported criteria by Bocquet *et al.*^{2 6 17 19} Our patient met all seven criteria of SCAR-J, which represent the most stringent criteria due to the fact that testing for HHV-6 reactivation is not widely available. We were able to perform indirect immunofluorescence testing (IFA) for HHV-6 as well as EBV at 2 weeks of illness. Most adults are infected with HHV-6 at young age and IFA testing for IgG nearly approaches 100% in adult at midlife. The elevated titres of either IgM or IgG correlate with either acute infection or reactivation of virus. However, absence of IgM antibody does not eliminate acute or recurrent infection. According to a study by Japanese group, HHV-6 IgG titre has been significantly increased in 62% of patients with DRESS.¹⁷ In our case, IgG titre was elevated to 1.40 (reference range <1.10) at 2 weeks. However, a second set of HHV-6 IgG level to trend the course and severity of the disease could not be done due to the loss of follow-up.¹⁶ EBV viral capsid antigen IgG, D early antigen as well as EBV nuclear antigen titres were high in this case suggesting a possible reactivation of virus.²⁰ Histological findings associated with DRESS are variable and not very specific.²¹ Common themes in the histopathology of DRESS are a dense superficial dermal infiltrate, denser than usual common drug eruptions that may be perivascular or band like, extravasated erythrocytes, dermal oedema and occasionally small granulomas in the superficial dermal infiltrate. Vacuolar alterations of the basal layer, spongiosis with parakeratosis and subcorneal pustule formation constitute epidermal changes.²² The biopsy from the present patient more closely resembles an urticarial drug eruption with focal interface dermatitis and mild purpura without vasculitis or significant epidermal change. Urticarial pattern seen in this patient's biopsy fits with the majority of cases published in the UK series by Walsh *et al.*²³ The mainstay of treatment for this syndrome is prompt recognition, withdrawal of the offending agent and supportive care. In case of severe organ involvement, corticosteroids, immunoglobulins and antivirals may have some therapeutic value.^{24–26} This case is a repeat illustration of phenytoin-induced DRESS. Given the high cross-sensitivity (40%–80%) among aromatic amines, such medications should be avoided in patients with previous reaction to any of the drugs within the group.

Patient's perspective

I suffer from symptoms of swelling throat which I informed the facility. I was at California Men's Colony, was treated with antibiotics at the facility and my symptoms did not get better. After waking up constantly to swelling throat, at 5–7 days later, I woke with my swollen throat and swelling of face like an elephant man. Since then I came to hospital, for last 3–5 days my symptoms has decreased. Since I have been here I have been treated with extraordinary care.

Learning points

- ▶ Drug rash with eosinophilia and systemic symptoms is rare but potentially life-threatening condition with high mortality rates.
- ▶ Diagnosis is challenging, and pathogenesis has not been entirely worked out.
- ▶ Herpes virus reactivation is considered a diagnostic marker and an indicator of the severity of illness.
- ▶ Prompt recognition and removal of offending agent remain the gold standard treatment.
- ▶ In cases of severe organ involvement, corticosteroids, immunoglobulins and antivirals may be helpful.

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Competing interests None declared.

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