Red Herring in Returned Traveler: Drug Reaction With Eosinophilia and Systemic Symptom (DRESS) Syndrome Mimicking Sepsis

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DOI: 10.1111/jtm.12152

We report a case of a 51-year-old Han Chinese recently returned traveler, who was admitted with a generalized maculopapular rash, fevers, shock, and multi-organ failure. Extensive investigations failed to reveal an infective cause. Skin biopsy findings together with the recent commencement of allopurinol raised a diagnosis of drug reaction with eosinophilia and systemic symptom syndrome. High-dose prednisolone was commenced and the patient made a rapid recovery. This case highlights that not all sepsis-like presentations in returned travelers are due to infective causes and that severe drug reactions need to be considered in the differential diagnosis.

Dermatoses have been reported by 8 to 10% of international travelers and commoner causes of febrile rash include viral (eg, arboviral infections and measles), bacterial (eg, rickettsial and typhoid), and parasitic infections and adverse drug reactions.1,2 Drug reaction with eosinophilia and systemic symptom (DRESS) syndrome is a rare, potentially fatal drug-induced hypersensitivity reaction that may include cutaneous manifestations, hematologic abnormalities, and involvement of liver, kidney, pancreas, eyes, lung, and heart.3,4 We report the case of a 51-year-old who presented with generalized maculopapular rash, fevers, and shock, following return from China.

Case Report

A 51-year-old East Timorese woman of Han Chinese ancestry, currently residing in Australia, presented with a 5-day history of generalized pruritic maculopapular rash, lethargy, anorexia, myalgia, and abdominal pain, 14 days after her return from a group tour to mainly rural Hunan and Sichuan, China. No other tour members had been unwell. Her regular medications included perindopril, pantoprazole, and vitamin D that she had been taking for over 12 months, and allopurinol 150 mg daily, commenced 3 weeks prior. Her past history included gout and chronic renal impairment (baseline serum creatinine 180 mmol/L) secondary to autosomal-dominant polycystic kidney disease. On examination, there was diffuse maculopapular rash with no evidence of lymphadenopathy or eschar. The patient was dehydrated and febrile (37.8°C) but hemodynamically stable, with generalized abdominal tenderness and bilaterally palpable polycystic kidneys. She was commenced on erythromycin by her general practitioner 2 days prior to admission, which was discontinued after two doses following the development of rash. She was unaware of her vaccination history. Initial investigations revealed a normal full blood examination (FBE) and liver function test (LFT) results, C-reactive protein 18.9 (normal <5 mg/L), and worsening renal impairment [serum creatinine 223 mmol/L (normal 44–80 mmol/L) and urea 13 mmol/L (normal 3.5–7.2 mmol/L)]. Nephrotoxic medications including allopurinol and ACE inhibitor were withheld.

Within 72 hours of presentation, she developed rigors, fevers to 40°C, and tachycardia, and became hemodynamically compromised with a fall in blood pressure to 77/50 mmHg. Despite aggressive fluid resuscitation, she remained hypotensive and became anuric. The
Figure 1 (A–C) Significant edema with generalized maculopapular rash. (D) Petechial hemorrhage in the oral mucosa.

patient was admitted to the intensive care unit for inotropic support and hemofiltration with a presumptive diagnosis of septic shock. She went on to develop marked peripheral edema, a worsening of her rash with the appearance of new petechial lesions on the buccal mucosa, and ulcers on her lower lip (Figure 1). Broad spectrum antibiotics including meropenem, vancomycin, and doxycycline were commenced, and she was extensively investigated for possible causes of infections that are common in travelers returning from China. Cultures of blood, urine, and feces were all negative.

She developed anemia and thrombocytopenia with her hemoglobin falling to 68 g/dL and platelets to 60 × 10^9/L. A hemolysis screen and hematologic studies were normal with a blood film showing marked neutrophilia, lymphocytosis with many atypical lymphocytes, eosinophilia, thrombocytopenia, and no evidence of fragments. There was evidence of disseminated intravascular coagulation with a raised INR of 2.1, prolonged activated partial thromboplastin time at 56 seconds, and low fibrinogen of 1.1. The white cell count increased sharply, peaking at 54 × 10^9/L with an associated neutrophilia (17 × 10^9/L), lymphocytosis (27 × 10^9/L), and eosinophilia (1.6 × 10^9/L—was 0.0 at admission). Her LFT became predominantly cholestatic (normal bilirubin 10 μmol/L, ALP 195 U/L, GGT 217 U/L, ALT 96 U/L, and AST 44 U/L) with associated synthetic dysfunction as evident with the elevated INR and hypoalbuminemia (24 g/L).

Screening for human immunodeficiency virus (HIV), hepatitis A/B/C/E, cytomegalovirus (CMV), Epstein–Barr virus (EBV), brucellosis, dengue fever, rickettsial, leptospirosis, measles, toxoplasmosis, typhoid fever, and schistosomiasis were negative. Malarial thick and thin films, Quantiferon Gold, polymerase chain reaction (PCR) for enterovirus, Hantavirus, human herpesvirus 6 (HHV-6), respiratory viruses (including influenza, respiratory syncytial virus, parainfluenza, adenovirus, metapneumovirus, and bordetella), and vasculitis screen (including antinuclear antibody, extractable nuclear antigen antibodies, anti-neutrophil cytoplasmic antibody, anti-double stranded DNA antibodies, and complement C3/C4) were also unremarkable. A chest X-ray showed small pleural effusions, and CT scan of abdomen was unremarkable other than bilateral polycystic kidneys.

In the absence of an infectious cause and having noted that she was commenced on allopurinol recently, a drug reaction was considered as the cause for her illness. The combination of the clinical features including cutaneous and hematologic abnormalities with peripheral eosinophilia in the setting of recent commencement of allopurinol raised the possibility of DRESS syndrome. A punch biopsy of the skin rash showed subepidermal vesicle formation and mild spongiotic dermatitis with an eosinophilic infiltrate in keeping with a bullous drug eruption similar to DRESS.

Given the known association of DRESS syndrome with HLA-B*58:01 in Han Chinese, HLA typing was performed and the HLA-B*58:01 haplotype was detected. The patient was commenced on systemic steroids whilst in intensive care, initially with a high dose of hydrocortisone (100 mg 6 hourly) and subsequently
oral prednisolone at 1 mg/kg after a week. Antibiotics were discontinued sequentially and she continued to improve. Her inpatient stay was further complicated by polyuric acute tubular necrosis, myocarditis (peak high sensitivity troponin T 5120, normal <15 ng/L), and pneumonitis. She recovered and was finally discharged after 31 days.

Discussion

The patient in this case was a returning traveler who presented with a febrile illness consistent with possible bacterial sepsis, malaria, or viral hemorrhagic fever including dengue and hantavirus. While the usual differential diagnoses for fevers in a returned traveler should be considered, it is also important to consider severe and potentially life-threatening drug reactions as possible causes.

The incidence of DRESS syndrome is estimated to be 1 per 1,000 to 10,000 drug exposures and the latency between drug exposure to disease manifestation is often long (2–6 weeks).3,4 The diagnosis of DRESS syndrome can be challenging especially given the prolonged latency from the time of drug exposure, particularly in this patient who had the confounding history of recent travel to East Asia.

The pathogenesis of DRESS syndrome is not well understood and further studies are required. There is a theory involving drug-specific immune response and herpesvirus reactivation, especially HHV-6.5–7 It has been postulated that a clinically unapparent viral reactivation triggers the expansion of a T-cell population which cross reacts with the drug, leading to cutaneous and visceral symptoms because of damage caused by activated cytotoxic CD8+ lymphocytes directed against the viral epitopes.7,8 Other herpesviruses such as HHV-7, EBV, and CMV have also been implicated.8 Interestingly, there have been cases of beta-lactam antibiotics possibly inducing flares of DRESS by increasing the replication of HHV-6.9 Whilst allopurinol seemed the most likely suspect, the macrolide could not be totally excluded as the causative agent, although there was no evidence of HHV-6, EBV, or CMV reactivation. Hence, the patient was advised to avoid both agents.

Other perpetrator drugs that have been identified include anti-epileptics, sulfonamides, and less commonly antivirals such as abacavir.5,10 The strong association between HLA-B*58:01 and allopurinol-associated severe cutaneous adverse reactions, up to 97-fold increased risk, has previously been validated in different populations including Han Chinese and Portuguese patients.11–14 This raises the question of whether prospective HLA typing should be done in at-risk populations being considered for certain drugs, given the strong association and severe sequelae. Furthermore, the incidence is reported to be higher in patients with chronic renal impairment.14

There is still a lack of consensus in the management of DRESS syndrome. The mainstream treatment is corticosteroids and the cessation of causative drug.3,15 Our patient was managed in a timely manner in association with multi-disciplinary specialties with a good outcome, especially given the previous reports of high fatality rates and prolonged relapse with allopurinol-associated DRESS syndrome.

Conclusion

This case illustrates that fevers and rash in travelers may be attributable to potentially life-threatening non-infective causes, and not just infections. Drug reactions like DRESS can mimic sepsis, hemorrhagic fevers, and other infections, and the consequence of being distracted by the red herring (travel in this case) could have potentially resulted in poor outcomes.

Declaration of Interests

The authors state that they have no conflicts of interest to declare.

References


J Travel Med 2014; 21: 425–428


