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DRESS syndrome presenting with acute hypoxic respiratory failure and delayed eosinophilia

Audrey Lee, Christopher Avanzato

Medicine, Albert Einstein College of Medicine, New York, New York, USA

Correspondence to
Dr Christopher Avanzato; zato317@gmail.com

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SUMMARY

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, yet life-threatening hypersensitivity reaction. It typically presents with fever, lymphadenopathy, eosinophilia and systemic organ dysfunction. Atypical presentations of DRESS syndrome, including elevated liver enzymes and acute respiratory distress syndrome, have previously been reported in rare cases. Here, we describe an otherwise healthy male patient in his mid-50s who presented with a rash, myalgia, shortness of breath and delayed eosinophilia that rapidly progressed to acute respiratory failure with hypoxia after starting trimethoprim-sulfamethoxazole. Prompt identification and treatment of atypical manifestations of DRESS syndrome is critical to reduce morbidity and mortality.

BACKGROUND

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe and life-threatening drug reaction that affects the skin and multiple internal organs. It is seen in 1 in 1000 to 10 000 drug exposures[1] with a mortality rate of up to 10%.[2] The onset and duration of DRESS are longer than other drug reactions, with symptoms presenting between 2 and 8 weeks following drug exposure.[3] Symptoms typically include fever, lymphadenopathy, acute rash, blood cell count abnormalities and involvement of at least one internal organ. Viral reactivation of human herpesvirus-6 (HHV-6), Epstein-Barr virus or cytomegalovirus is also commonly seen in DRESS syndrome.[4]

The RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions) scoring system is used to determine the probability of DRESS syndrome.[2] Depending on the score, cases of DRESS are categorised as no case, possible case, probable case or definite case. The Japanese drug-induced hypersensitivity syndrome (DIHS) criteria include reactivation of HHV-6 as an additional criterion and classify cases as either typical or atypical.[5] Finally, Bocquet's criteria are based on the presence of skin eruption, blood eosinophilia or the presence of atypical lymphocytes and internal organ involvement, including lymphadenopathies, hepatitis, interstitial nephritis, interstitial pneumonia or carditis. A diagnosis of DRESS syndrome using Bocquet's criteria requires the presence of all three features.[6]

DRESS syndrome has been previously described in patients after taking a variety of medications, with non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsants and antibiotics being the most common culprits.[7] The incidence of DRESS syndrome in the setting of trimethoprim-sulfamethoxazole (TMP-SMX) is an estimated 1 in every 1000 to 10 000 exposures, with antibiotics attributed to 74% of cases and sulfonamides compromising 3% of these cases.[8] However, over 40 medications have been implicated in the development of DRESS syndrome. Atypical DRESS syndrome can present without meeting the diagnostic criteria and therefore requires a high level of clinical suspicion. Here, we present a severe case of atypical DRESS syndrome caused by TMP-SMX that manifested with a rash and unusually extensive lung involvement.

CASE PRESENTATION

A man in his early 50s with no significant medical history presented with a 3 day history of shortness of breath, cough and diffuse petechial rash affecting the face, trunk and bilateral lower extremities. Three days after completing a 10–14 day course of TMP-SMX for a urinary tract infection, he developed chills, sweats and myalgias with an associated metallic taste. He denied taking any medications for these symptoms, including NSAIDs. Three days prior to admission and 5 days after completing the course of TMP-SMX, he developed a non-pruritic rash over the trunk and bilateral lower extremities. The next day, he developed a cough and shortness of breath. The shortness of breath progressively worsened, which prompted his visit to the emergency department. He denied any allergies to medications and any previous adverse drug reactions. He denied a sulfa allergy, prior allergic reactions, adverse reactions to medications or drugs and a family history of similar reactions.

On presentation, the patient was afebrile and had an oxygen saturation (SpO_2) of 87% on room air. He was immediately started on 4 L nasal cannula. On physical examination, a diffuse macular erythematous rash was noted on the face and trunk, and a petechial rash was noted on the bilateral lower extremities. No lymphadenopathy was appreciated. Pulmonary examination was notable for left basilar rales with no increased work of breathing or use of accessory respiratory muscles. Over the course of the hospitalisation, the petechial rash spread to the patient's bilateral upper extremities.

Investigations

Initial laboratory results showed normal white blood cell count, normal platelet count and no atypical lymphocytes on the white blood cell differential. Eosinophilia was absent on admission; however,

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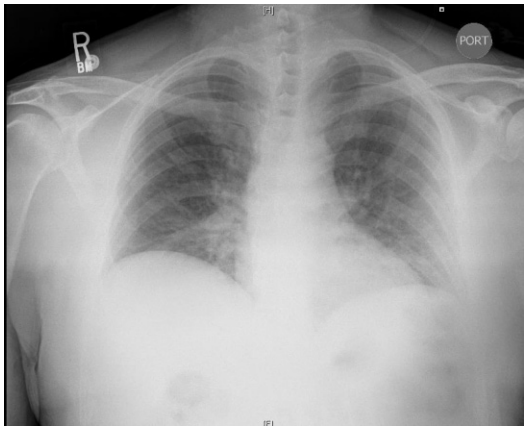

Figure 1 Chest X-ray on admission showing hazy opacities.

the patient developed eosinophilia 2 weeks after initial presentation, on hospital admission day 14, with eosinophils noted to be elevated at 1.1 k/uL at that time. Eosinophils remained elevated for the rest of the patient's hospital stay. Urine microscopic analysis was notable for few bacteria and elevated white blood cells. Liver tests on admission were notable for an elevated aspartate aminotransferase to 74 and an elevated alanine aminotransferase to 234. Creatine kinase was normal. Aldolase was checked 2 weeks into admission and was elevated to 10.9. Procalcitonin was normal. A chest X-ray on admission showed hazy opacities bilaterally (figure 1). CT of the chest showed ground-glass opacities with emphysematous changes (figure 2). One day later, a repeat chest X-ray was notable for worsening hazy and interstitial pulmonary opacities likely due to worsening inflammatory lung disease (figure 3). Using the RegiSCAR scoring system, this patient was placed in the 'possible case' category with a score of 4 (table 1). He was classified with atypical DRESS using the Japanese DIHS criteria given the lack of HHV-6 reactivation, lack of fever and lack of blood cell count abnormalities.[9] The patient met Bocquet's criteria given the presence of a rash consistent with reaction, internal organ involvement and eosinophilia, although the presence of eosinophilia was delayed.

Extensive infectious workup was negative, including respiratory pathogen panel, HIV, hepatitis B and C, and many fungal pathogens. Cytomegalovirus on bronchoalveolar lavage (BAL) was negative, as well as plasma Epstein-Barr virus and HHV-6. HHV-7 and HHV-8 were not tested. Of note, BAL was positive for herpes simplex virus-1 (HSV-1) with a viral load of 171 000, and the patient was started on acyclovir. It is unclear if this was

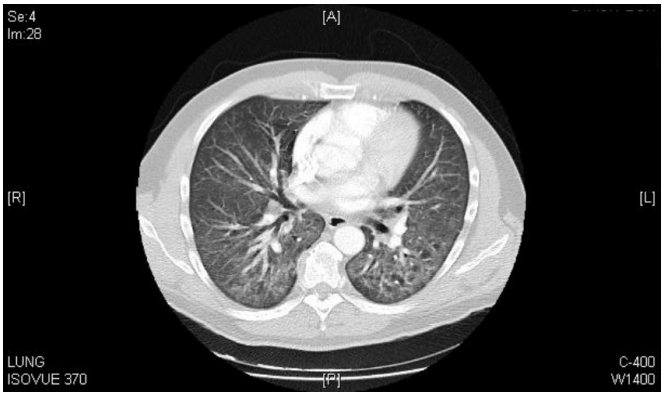

Figure 2 CT of the chest on admission showing ground glass opacities with emphysematous changes.

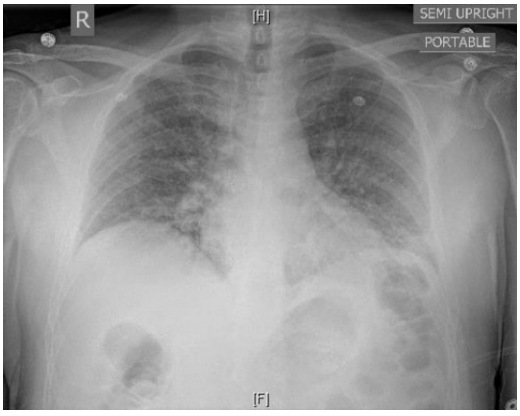

Figure 3 Chest X-ray on hospital day 1 showing worsening hazy and interstitial pulmonary opacities favoured to be due to worsening inflammatory lung disease.

due to immunosuppression from steroids or reactivation of HSV associated with DRESS syndrome. Additionally, a thorough autoimmune workup was also negative. Serum protein electrophoresis did not detect monoclonal protein. Peripheral flow cytometry was negative.

The inflammatory work-up was significant for elevated C reactive protein to 12.1 mg/dL, elevated lactic dehydrogenase to 669 U/L, elevated fibrinogen to 641 mg/dL and elevated ferritin to 7040 ng/mL.

Differential diagnosis

DRESS typically presents after 2 weeks of exposure to the offending agent since it is a delayed hypersensitivity reaction. Given the patient's clinical presentation and laboratory findings, DRESS was diagnosed. The differential diagnosis for this case is broad and includes consideration of infectious, inflammatory, autoimmune and malignant aetiologies. Infectious workup was notable for HSV-1 on BAL and the patient presented with respiratory symptoms; however, given the lack of other infectious symptoms and the presence of other organ involvement, it was deemed unlikely that HSV-1 was the primary cause of the patient's presentation, and rather reactivation of HSV-1 was either due to immunosuppression from steroids or reactivation associated with DRESS syndrome. Given the elevated ferritin, secondary haemophagocytic lymphohistiocytosis (sHLH) as a complication of DRESS was also considered. Other medication

Table 1 Patient's signs and symptoms using various DRESS scoring criteria

RegiSCAR score for DRESS	
Fever (≥38.5°C)	No (–1)
Enlarged lymph nodes (≥2 sites, >1 cm)	No (0)
Atypical lymphocytes	No (0)
Eosinophilia	Yes (+1)
Skin rash extent >50%	Yes (+1)
At least two of: oedema, infiltration, purpura, scaling	Yes (+1)
Biopsy suggesting DRESS	Unknown (0)
Internal organ involvement	Yes, ≥2 (+2)
Resolution in >15 days	No/Unknown (–1)
Alternative diagnoses excluded (by ≥3 biological investigations)	Yes (+1)

DRESS, drug reaction with eosinophilia and systemic symptoms; RegiSCAR, European Registry of Severe Cutaneous Adverse Reactions.

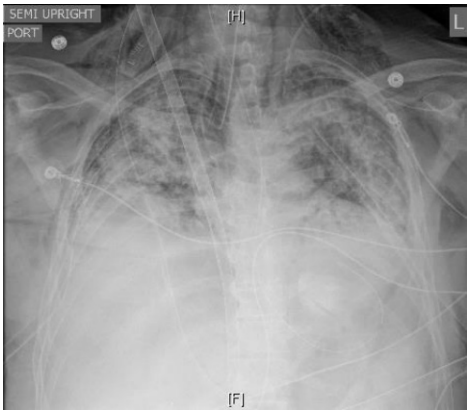

Figure 4 Chest X-ray on hospital day 23 showing extensive bilateral airspace opacities compatible with acute respiratory distress syndrome/multifocal pneumonia.

culprits were effectively ruled out as the patient denied taking any of the other medications, including NSAIDs, prior to presentation. The patient had negative autoimmune and malignancy work-ups, which decreased the likelihood of these aetiologies.

TREATMENT

In addition to supportive care, empiric treatment with systemic steroids was initiated. While on the floor, the patient's oxygen saturation failed to improve with supplemental oxygen. He was transitioned to a non-rebreather mask without significant improvement in SpO_2 levels. At this point, he was started on a high-flow nasal cannula. Given his rapidly increasing oxygen requirements, he was transferred to the intensive care unit (ICU) under the care of a multidisciplinary team approach.

While in the ICU, an additional chest X-ray showed extensive bilateral airspace opacities despite supplemental oxygen (figure 4). Furosemide was given for pulmonary oedema. Bronchoscopy was performed and showed no significant abnormalities. Ultimately, the patient required intubation and veno-venous extracorporeal membrane oxygenation (VV ECMO). A right-sided, transbronchial lung biopsy was performed and was notable for non-specific signs of fibrosis and inflammation. While in the ICU, the patient rapidly deteriorated.

OUTCOME AND FOLLOW-UP

Despite maximal medical therapy, the patient continued to have desaturations while on full ventilator and full ECMO settings. He experienced persistent hypoxia and developed worsening hypotension despite pressor support. Autopsy showed that the cause of death was cardiopulmonary failure secondary to long-term therapy complications and blood loss.

DISCUSSION

The incidence of DRESS syndrome is low; however, this may be attributed to under-reporting and unawareness. The mechanism and pathogenesis have not been clearly elucidated but likely involve genetic predisposition, accumulation of drug metabolites and drug-virus interactions.[2 3 6] Diagnosing DRESS syndrome requires a high level of clinical suspicion, as identifying the qualifying features is challenging. The RegiSCAR scoring system, Japanese DIHS criteria and Bocquet's criteria are commonly used to delineate the likelihood that a patient has DRESS.[10] Given the non-specific symptoms and multiorgan involvement seen in both typical and atypical presentations of DRESS, the differential diagnosis is quite broad, and clinicians should consider this syndrome until other aetiologies have been ruled out.

Antibiotic sulfonamides have been previously reported as common causative agents of DRESS syndrome, and there was a temporal relationship between taking TMP-SMX and our patient's presenting symptoms. His hospital course highlights the life-threatening nature of DRESS syndrome as pulmonary manifestations may be a presenting sign of DRESS and are frequently misdiagnosed for pneumonia. Because our patient lacked the characteristic features of DRESS syndrome, he was diagnosed with DRESS. Prior retrospective studies have shown that the liver is the most commonly affected organ in DRESS.[11] In our review of the literature, we found one case report that describes atypical DRESS syndrome in a patient presenting with transaminitis.[12] One systematic review highlighted the pulmonary manifestations of DRESS, which are rare but associated with a more severe clinical course and worse outcomes. The review mentions one case of pulmonary DRESS secondary to TMP-SMX in a male patient with other pulmonary co-comorbidities.[13] To our knowledge, there are no case reports that describe DRESS syndrome induced by TMP-SMX that presents with acute respiratory failure with hypoxia in an otherwise healthy adult with delayed eosinophilia.

The most common pulmonary radiographic findings in DRESS are interstitial infiltrates seen in 50% of cases, followed by acute respiratory distress syndrome in 31% of cases.[13] Shortness of breath and cough are also common pulmonary symptoms seen in DRESS. In this case, the patient presented with acute hypoxic respiratory failure and was found to have ground-glass and emphysematous changes of the lungs on CT chest.

Despite treatment with systemic steroids and maximal supportive care, our patient still developed cardiopulmonary failure. One possibility for this outcome is an intense delayed hypersensitivity reaction involving inflammatory cytokines that led to severe lung damage. Additionally, the patient reported completing the course of TMP-SMX despite symptoms of rash and myalgia after starting the medication. The continuation of TMP-SMX despite signs of an adverse reaction may have worsened the initial presenting symptoms. Another possibility is the use of furosemide during the hospital course. Prior case reports describe DRESS syndrome secondary to furosemide.[14] Although unlikely, the use of this medication may have exacerbated the pulmonary manifestations of DRESS. It is important to note that the delayed onset of asynchronous and discontinuous features may have also contributed to this poor outcome.

There are no randomised controlled trials to date that guide treatment of DRESS syndrome. In general, first-line management involves discontinuation of the suspected offending agent and initiation of glucocorticoids. In mild to moderate cases without visceral organ involvement, topical steroids are used for rash. However, in more severe cases associated with visceral involvement, systemic steroids are used.[15] Alternatives to corticosteroids, including the use of calcineurin inhibitors such as cyclosporine, are being explored, particularly in patients who are unable to sustain prolonged immunosuppression.[16]

Our case highlights the variability and severity in the presentation of DRESS syndrome. The sequelae of DRESS syndrome range from full recovery to even death, as demonstrated by this case. Patients should be properly counselled when prescribed medications that are known to be associated with DRESS to promptly call their provider if they develop a rash, fever or start to feel unwell. DRESS can present without the presence of particular features, and given the asynchronous nature of its

presentation, it can be difficult to recognise on presentation. Early recognition and treatment of DRESS is imperative to lower mortality and improve outcomes.[17] Given the severity of the manifestations of DRESS, awareness of this syndrome with early identification followed by appropriate management and close follow-up is necessary to minimise morbidity and mortality.[18 19]

Learning points

- This is a case of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with severe pulmonary manifestations in an otherwise healthy patient with delayed eosinophilia.
- DRESS syndrome varies in presentation and severity. Therefore, high clinical suspicion can lead to prompt identification and initiation of treatment with systemic glucocorticoids and supportive care.
- Given the lethality of DRESS syndrome, starting treatment as soon as possible is crucial to reduce the risk of mortality and improve prognosis.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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