CASE REPORT

Extensive pulmonary involvement with raltegravir-induced DRESS syndrome in a postpartum woman with HIV

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SUMMARY

An 18-year-old postpartum woman with HIV, on lamivudine–zidovudine, lopinavir–ritonavir and raltegravir, presented with a 1-week history of rash and fevers. Initially admitted to obstetrics and gynaecology service for treatment of possible endometritis, she was transferred to the HIV medicine service for high fever, respiratory distress, hypotension and tachycardia. On admission, she was febrile (102°F) with findings of cervical and submandibular lymphadenopathy, diffuse morbilliform rash, generalised pruritus, facial oedema, and oedematous hands and feet. Consultations to various specialty services were initiated to rule out infectious, dermatological, rheumatological and drug-induced aetiologies. On the fourth day of hospitalisation, laboratory findings of significant eosinophilia and hepatitis (alanine aminotransferase 147 IU/L and aspartate aminotransferase 124 IU/L), in conjunction with the identification of the timing of medication use, led to a diagnosis of DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome secondary to raltegravir. After discontinuing raltegravir and starting prednisone, her DRESS symptoms completely resolved.

BACKGROUND

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an uncommon but potentially life-threatening hypersensitivity reaction commonly associated with anticonvulsants. Although DRESS has also been documented in association with antiretroviral therapy (abacavir,^{1–5} nevirapine^{6–11} and efavirenz^{12–13}) for HIV-1, there have only been two reported cases associated with raltegravir.^{14–15} Additionally, pulmonary involvement is a rare clinical characteristic of DRESS syndrome (present in only 5% of the 151 cases evaluated in a systematic review of DRESS syndrome case reports¹⁶). We report a case in an 18-year-old postpartum woman with HIV who received raltegravir as part of a combination antiretroviral therapy for treatment of HIV. This case demonstrates that DRESS syndrome may be associated with raltegravir and may have pulmonary involvement that was not commonly seen previously.

CASE PRESENTATION

An 18-year-old woman with a CD4 count of 692 cells/mm³ (35%), HIV viral load of 23 copies/mm³ who was diagnosed with HIV in July 2012 during a routine obstetric visit in Mexico and started on highly active antiretroviral therapy with

lamivudine–zidovudine and lopinavir–ritonavir had raltegravir added to her treatment regimen on 23 December 2012 for intensification of her regimen due to low-level viremia near the time of delivery. On 11 January 2013, she had a complicated vaginal delivery (postpartum haemorrhage, urinary retention and chorioamnionitis treated with ampicillin and gentamicin). On 29 January 2013, 6 weeks after adding raltegravir, she presented to the emergency department with a 1-week history of worsening rash and persistent fevers. The patient was initially admitted to the obstetrics and gynaecology service given her history of complicated delivery and for treatment of possible endometritis. On arrival, she presented with high-grade fever (102°F), tachycardia (heart rate 120), hypotension (blood pressure 94/45), tachypnoea (respiratory rate 21), and physical examination findings significant for cervical and submandibular lymphadenopathy, diffuse morbilliform rash, generalised pruritus, facial oedema, and oedematous hands and feet. On hospital day 1, she was subsequently transferred to the HIV medicine service for a concerning clinical picture consistent with sepsis and was started empirically on vancomycin and piperacillin–tazobactam for broad coverage. Dermatology and infectious disease services were also consulted regarding her diffuse morbilliform, pruritic, blanching rash covering her face, trunk and extremities in addition to documented fevers. A broad infectious evaluation was initiated given the high suspicion of sepsis. After her transfer to the HIV medicine service, the patient's vital signs, notwithstanding her high-grade fever, returned to normal. Laboratory results were significant for macrocytic anaemia (haemoglobin 11.4 g/dL and mean corpuscular volume 118.4 fL) and elevated eosinophils (800/mm³). Additionally, her chest X-ray was notable for right basilar and retrocardiac opacity with trace right pleural effusion (figure 1). A subsequent chest CT revealed pulmonary nodules in right and left upper lobes concerning for tuberculosis (TB; figure 2). The patient was placed in respiratory isolation given high suspicion for TB as a result of her imaging studies, history of positive QuantiFERON, residency in Mexico and a positive childhood history of TB previously treated with isoniazid.

INVESTIGATIONS

The following day after her transfer, the patient continued to have macrocytic anaemia and elevated

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Figure 1 Chest X-ray demonstrating right basilar and retrocardiac opacity with trace right pleural effusion.

eosinophilia ($1300/\text{mm}^3$) without other laboratory derangements. Zidovudine was believed to be the cause of her macrocytic anaemia, so the medication was stopped and her macrocytic anaemia subsequently resolved. Given her initial presentation with a septic picture and elevated eosinophils, a broad infectious evaluation was initiated with the resulting serologies and cultures negative for: cytomegalovirus, Epstein-Barr virus (EBV), *Chlamydia*, viral hepatitis A–D, adenovirus, influenza, parainfluenza, respiratory syncytial virus, *Coccidioides*, histoplasma, *Cryptococcus*, *Strongyloides*, *Cryptosporidium*, *Cyclospora* and microsporidia. Although the patient did have a positive antinuclear antibody (1:640), a comprehensive rheumatology evaluation (double-stranded DNA, anti-Smith antibody, anti-Sjögren syndrome type A antigen, and anti-Sjögren syndrome type B antigen) was unremarkable for systemic lupus erythematosus as being a possible cause of her presentation. She was subsequently ruled out for TB with three negative sputum acid-fast bacillus (AFB) smears/cultures and two negative sputum TB PCR tests. Given her pulmonary nodules, malignancies, such as lymphoma, were also considered and an initial bronchoscopy with bronchoalveolar lavages was performed and was unremarkable.

Figure 2 Chest CT with contrast demonstrating acinar nodules in the left upper lobe and subpleural nodules in the right lower lobe as well as bibasal atelectasis and a small right pleural effusion.

Bronchoscopic biopsies, however, were not performed by pulmonary consultation service. Of note, lymphoma was also less likely given a normal B-cell lymphoma panel. On hospital day 3, she was noted to have a new mild hepatitis with an elevated alanine aminotransferase and aspartate aminotransferase of 147 IU/L and 124 IU/L, respectively. The cause of her persistent eosinophilia was unclear and the patient denied use of new soaps, detergents or medications other than the addition of raltegravir in December 2012. Based on the exclusion of other potential causes, as well as these new biochemical findings, a diagnosis of DRESS syndrome was made and raltegravir was identified as the most likely cause given the temporal relationship of her clinical symptoms and timing of the initiation of raltegravir. Additionally, a literature review revealed two prior cases of DRESS associated with raltegravir.^{14 15} Of note, the pulmonary nodules were suspected to be secondary to DRESS syndrome versus an infectious process as all cultures were unrevealing.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for our patient's overall clinical presentation was initially broad and included allergic and/or drug reactions, autoimmune (systemic lupus erythematosus, scleroderma, vasculitis), infections including bacterial aetiologies (*Staphylococcus*, *Streptococcus*, syphilis), viral aetiologies (EBV, adenovirus), fungal aetiologies (*Cryptococcus*, coccidioidomycosis, histoplasmosis), parasitic (*Strongyloides*, scabies), malignant (Hodgkin's lymphoma, Castleman's disease) aetiologies and HIV-related immune reconstitution inflammatory syndrome. These possibilities were all investigated thoroughly through extensive laboratory testing. Multiple specialty services were consulted (dermatology, rheumatology, pulmonology and infectious disease) to assist in narrowing and obtaining the diagnosis. In addition, the onset of our patient's symptoms occurred about 5 weeks after initiation of raltegravir, which was consistent with the delayed timing of DRESS syndrome.¹⁶ In an effort to more accurately diagnose the DRESS syndrome, our primary team utilised a scoring system, the RegiSCAR (a European registry of severe cutaneous adverse reaction (SCAR)), to assist in the diagnosis.¹⁷ For the diagnosis of DRESS: fever (0 points), enlarged lymph nodes (1 point), eosinophilia (24%; 1 point), >50% skin rash extent (1 point), liver and lung involvement (2 points; 1 per organ), and all other diagnoses had been excluded (1 point). Based on this scoring system,¹⁷ our patient met the criteria of a 'definite case', with a final score >5. Finally, after an extensive consultation with our multispecialty teams, it was ultimately agreed on by all involved that raltegravir-induced DRESS syndrome was the most likely cause of this patient's clinical picture.

TREATMENT

Once the diagnosis of DRESS was made, as recommended by dermatology, the offending agent, raltegravir, was discontinued and the patient was placed on hydroxyzine 10 mg at night and started on a steroid taper of prednisone 60 mg.

OUTCOME AND FOLLOW-UP

As a result of the cessation of raltegravir and her treatment with hydroxyzine and prednisone, the patient's rash, fever and hepatitis completely resolved. Her antiretroviral therapy was switched to emtricitabine–tenofovir and lopinavir–ritonavir, which she tolerated without adverse events. However, she chose to leave the hospital against medical advice and was inconsistently adherent to her antiretroviral medications in addition to her steroid treatment for her DRESS syndrome and had a relapse with cutaneous findings of pruritic rash. She was

promptly treated with reinstitution of prednisone 30 mg with subsequent resolution of her rash. As of June 2013, she remains off antiretroviral therapy by choice, but is taking prednisone 5 mg daily without further symptoms or signs of raltegravir-induced DRESS syndrome.

DISCUSSION

Our patient's clinical presentation is consistent with other published case reports of medication-induced DRESS syndrome. Although raltegravir-induced DRESS syndrome is highly uncommon, our is the third documented case,^{14 15} which highlights the possibility that raltegravir may be associated with DRESS syndrome more often than previously believed.

Given its potent *in vitro* activity against wild-type as well as multidrug-resistant HIV, raltegravir is an HIV integrase inhibitor commonly used in combination therapy against wild-type as well as multidrug-resistant HIV.^{18–20} In our patient's case, raltegravir was added to her regimen of lamivudine–zidovudine and lopinavir–ritonavir for intensification of her regimen due to low-level viremia near the time of delivery after extensive consultation with HIV physicians, clinical pharmacists and obstetricians involved in the patient's clinical management. While an intensification strategy is not recommended by international guidelines, it is sometimes used by clinicians in special situations. It was agreed on by her entire medical team that the benefit of intensification of her regimen with raltegravir (reducing HIV viremia at the time of delivery to hopefully prevent HIV transmission to the infant) outweighed the risk of the potential toxicities of the addition of raltegravir. However, this case highlights the potential toxicity of an intensification strategy, even with a medication that is deemed by many HIV-experienced providers as being fairly well tolerated with minimal side effects seen in clinical practice.^{18 20 21}

Evidence supporting raltegravir as the aetiological cause in our case consists of multiple factors. First, there are no published cases of DRESS syndrome associated with the use of zidovudine, lamivudine and lopinavir.¹⁶ Second, the timing and symptoms are consistent with the presentation of DRESS syndrome. Third, with the occurrence of this case, there will now be three published cases of raltegravir-induced DRESS syndrome suggesting a possible emerging correlation between this hypersensitivity reaction and the use of raltegravir. Finally, the patient was immunocompetent with a high CD4 cell count of 692 cells/mm³. High CD4 cell count was also observed in a previous case report of raltegravir-induced DRESS syndrome.¹⁵ This association has been studied more extensively in nevirapine-induced DRESS syndrome, suggesting that CD4 cells may promote skin rash and hepatotoxicity with certain medications.^{21 22} However, causality between high CD4 count and raltegravir requires further investigation.

Although the pathogenesis of raltegravir-induced DRESS syndrome has not been elucidated, HIV infection is associated with a hyperallergic state and very high incidence of immune-related hypersensitivity reactions.¹⁹ This hypothesis of increased atopy seen in HIV-infected patients and its potential pathogenesis in antiretroviral-related DRESS syndrome will need to be further explored in future studies. Of note, as combination antiretroviral agents are increasingly developed into single pill formulations to improve patient adherence, it is becoming more important to provide clinicians with greater awareness of these less common drug-related reactions.¹⁹

Unlike previous case reports of raltegravir-induced DRESS syndrome, our patient presented with extensive pulmonary involvement. Pulmonary involvement is a rare clinical

characteristic of DRESS syndrome, present in only 5% of the 151 cases evaluated in a systematic review of DRESS syndrome case reports. Although drug-induced pulmonary injury most often demonstrates interstitial lung damage, alveolar damage or vasculitis involvement,²³ this patient did not exhibit any of these findings on imaging studies. Although a bronchoscopy was performed, only bronchoalveolar lavages were done. No bronchoscopic biopsies were obtained by the pulmonology service (by choice) at the time of the initial bronchoscopy, which would have been helpful in ruling out other possibilities and for further confirmation of this diagnosis. However, other potential causes of these nodules have thus far been unlikely given the negative laboratory and imaging results. As such, the current hypothesis is that these nodules are most likely secondary to DRESS. Although our patient did have a history of TB treated in her childhood and presented with a positive QuantiFERON test, she did not have the clinical manifestations of TB and she also tested negative on consecutive AFBs, TB PCR and bronchoalveolar lavage. Nodule biopsy was planned but had not yet been performed by the time of manuscript submission.

Further studies to fully characterise the link between raltegravir and DRESS syndrome, particularly with significant pulmonary involvement, are needed.

Learning points

- ▶ We report an unusual case of raltegravir-associated drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with extensive pulmonary involvement.
- ▶ Clinicians should be aware of the signs and symptoms consistent with DRESS syndrome (drug reaction, eosinophilia, systemic symptoms), since this severe drug-induced hypersensitivity reaction may mimic other systemic diseases.
- ▶ Despite its tolerability, raltegravir should be monitored closely because of the potential for possible life-threatening reactions manifesting as cutaneous, liver and pulmonary involvement.
- ▶ The RegiSCAR scoring system is a helpful tool to help guide a differential diagnosis and allow for prompt recognition and appropriate treatment.
- ▶ With the addition of this case, the mounting evidence suggests that clinicians should be more aware of the association with raltegravir-induced DRESS syndrome given that raltegravir is commonly prescribed in antiretroviral treatment-naïve as well as treatment-experienced patients with HIV.

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Competing interests None.

Patient consent Obtained.

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