CASE REPORT

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome secondary to antituberculosis drugs and associated with human herpes virus-7 (HHV-7)

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SUMMARY

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a serious reaction to drugs with a clinical presentation of rash, fever, lymph node enlargement and internal organ involvement. Reports have described the reactivation of human herpes virus 6 (HHV-6) and other HHVs in association with this syndrome. We report a 41-year-old woman who developed a rash, fever, liver dysfunction, eosinophilia and atypical monocytosis 21 days after initiation of the quadruple therapy for tuberculous cervical lymphadenitis. HHV-7 DNA was detected in blood by PCR suggesting infection with or more likely reactivation of HHV-7 as a contributing factor or consequence of this serious adverse drug reaction.

BACKGROUND

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an important diagnosis to consider in drug hypersensitivity reactions. Visceral involvement differentiates this syndrome from other cutaneous hypersensitivity reactions and it may include hepatitis, arthritis, pulmonary infiltrates and interstitial nephritis.¹ These visceral manifestations are life-threatening, giving DRESS a mortality rate of approximately 10%.

DRESS has been estimated to occur in 1 in every 10 000 exposures to drugs, the most common of which are antiepileptics, allopurinol and sulfonamide antibiotics. There are very few reports of DRESS associated with antituberculosis (TB) medication. Although there are conflicting views on the pathogenesis of DRESS, recent studies have suggested a close relationship between the reactivation of human herpes virus 6 (HHV-6) and the development of DRESS.²⁻³ Sporadic reports describe the reactivation of other herpes viruses such as HHV-7, Epstein-Barr virus (EBV) and cytomegalovirus during the course of the disease.⁴

CASE PRESENTATION

A 41-year-old woman with tuberculous cervical lymphadenitis had been treated with first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide and ethambutol). Twenty-one days after starting treatment, she developed fever of over 38 °C, a non-pruritic maculopapular rash, myalgia and lethargy. She had no other medical history and was not

on any regular medication: prescribed, herbal or over the counter.

Physical examination only revealed a florid maculopapular rash all over her body, which had become confluent in areas. The pre-existing enlarged lymph node in her cervical chain secondary to tuberculous adenitis was palpable. All four antituberculous drugs were stopped at day 24.

INVESTIGATIONS

At presentation, the only abnormality was a C reactive protein (CRP) of 58 mg/L and mildly deranged liver function tests (LFT): alanine transaminase (ALT) 38 IU/L and aspartate aminotransferase (AST) 45 IU/L. Four days after discontinuing TB medication, the CRP reduced to 20 mg/L; however, the LFTs deteriorated: bilirubin 8 µmol/L, ALT 427 IU/L, AST 643 IU/L, alkaline phosphatase 149 IU/L, γ-glutamyl transpeptidase 501 IU/L, albumin 39 g/L, international normalised ratio 1.0. The full blood count revealed a high total white cell count (WCC) 15.78 with lymphocytosis 7.08, monocytosis 2.52 and an eosinophilia 0.95.

PCR of plasma was performed to detect EBV, cytomegalovirus (CMV), HHV-6 and HHV-7; only HHV-7 DNA was detected, indicating an HHV-7 viraemia. Additional serological investigations showed no evidence of acute infections with hepatitis A, hepatitis B, hepatitis C, hepatitis E, EBV or CMV. The negative viral hepatitis screen together with sterile blood cultures and absence of antinuclear antibodies helped ruling out other potential causes of symptoms.

TREATMENT

All four antituberculous drugs were stopped at day 24. The patient's symptoms and blood tests were closely monitored thereafter. Within 48 h of the peak abnormality in the blood tests, CRP, WCC and LFTs started to improve and, therefore, other than stopping the offending agents, no other treatment was implemented.

OUTCOME AND FOLLOW-UP

The fever began to settle a few days after stopping medication, and the rash, lethargy and myalgia continued for a couple of weeks before slowly resolving.

Thirty-five days after all medication was stopped, a step-wise reintroduction antituberculous therapy

To cite: Draz N, Datta S, P Webster D, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-010348

was attempted. Ethambutol was the first to be initiated as it was thought to be the least likely offending agent. However, within 5 h of taking the first dose, the fever and rash recrudesced. Blood tests at this time showed only a mild derangement of liver function tests. Repeated viral serology and PCR revealed only HHV-7 viraemia. The patient stopped taking the medication and the symptoms settled within 3 days.

Sequential reintroduction of isoniazid, ethambutol and rifabutin (rather than rifampin to try and reduce any cross-reactivity) has been reattempted, but each drug on each occasion has led to rapid occurrence of high fever and rash requiring cessation of the drug. The patient is currently clinically well with no evidence of active TB and the lymph node has completely resolved, so the patient has elected not to have any further treatment at the moment, but remains under regular review.

DISCUSSION

Symptoms of DRESS begin 2–6 weeks after the onset of drug intake and may persist for several weeks after drug withdrawal. To diagnose and differentiate DRESS as a separate entity from other severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome or toxic epidermal necrolysis, a European registry for severe cutaneous adverse reaction was developed, called RegiSCAR.⁵ In this, diagnostic criteria for DRESS have been established. Patients must have three of the four following main criteria: an acute rash, fever above 38 °C, lymphadenopathy at two sites, involvement of at least one internal organ and abnormalities in lymphocyte and eosinophil counts. Additional criteria include hospitalisation and that the reaction is suspected to be drug-related. The RegiSCAR scoring system defines a case of suspected DRESS as 'no,' 'possible,' 'probable' or 'definite' case. Our patient had a score greater than 5, and therefore was a 'definite' case of DRESS according to these criteria.^{1 2 5}

Several clinical similarities can be observed between DRESS and infectious mononucleosis, suggesting a possible range of viruses as triggers for this syndrome. DRESS has unique features that are not necessarily typical of a drug reaction. These include (1) late onset in relation to introduction of the causative medication, (2) clinical signs and laboratory values suggesting a viral infection and (3) episodes of exacerbation, despite withdrawal of the offending drug. HHV-6 reactivation has been described in several studies of patients with DRESS syndrome.^{1 2 6} Therefore a Japanese consensus group has developed a second set of criteria for DRESS which encompasses the reactivation of HHV-6 as an additional criterion.^{5–7} However other herpes virus infections such as EBV or CMV and coreactivation of HHV-6 and HHV-7 have also been reported in cases of DRESS. Yet this case showed no reactivation of, or infection by, any herpes virus other than HHV-7. This finding has only been reported in two other case reports, both of which were due to carbamazepine therapy.^{8 9} The exact pathogenesis of DRESS remains under debate. Although human leucocyte antigen type and pharmacogenetics may have a role, it is felt that perhaps drugs can promote reactivation and replication of latent viruses, which then have the capacity to infect T cells and induce ectopic expression of CD4, leading to dysregulation of CD8 lymphocytes. These activated cells produce large quantities of cytokines, which are the key mediators that promote the symptoms of DRESS even after the medication has been stopped.^{10 11}

There are no guidelines available for the management and treatment of DRESS, partly due to its unknown pathogenesis. In all case reports the offending drugs were stopped and, in some, corticosteroids were used. However there is insufficient evidence

to ascertain whether corticosteroids are beneficial. In this case, corticosteroids were not prescribed. After stopping her medication she was closely monitored and it was clear that the symptoms and abnormal blood tests were settling on without further intervention.

The cases most commonly associated with DRESS were caused by antiepileptics, sulfur containing compounds and allopurinol.^{2 11 12} However, antibiotics have also been indicated.^{1 13–15} The treatment for drug susceptible TB is standardised: isoniazid, rifampicin, ethambutol and pyrazinamide in the initial phase of treatment, and then isoniazid and rifampicin alone in the continuation phase after 2 months. There are few alternative anti-TB medications, all of which necessitate a longer course of treatment in an already arduous regime with significant potential side effects. Therefore, developing DRESS leads to significant interruptions in TB treatment and a dilemma as to which antituberculous agents can be given next.^{13 15} It is difficult in the context of antituberculous medication, where four different medications are started together, to ascertain a single offending agent. Interestingly, if DRESS had developed due to the combination of antituberculous treatment, reintroduction of any one of the four medications can cause a resurgence of symptoms. In a recent case series, patients' TB treatment was suspended during the course of DRESS, which was treated with steroids.¹³ Once the DRESS symptoms had resolved, a new treatment regimen similar to that used for multi-drug resistant TB was initiated slowly.^{13 15} The most common offending agent was rifampicin, and when restarting antituberculous medication levofloxacin was the best tolerated.^{13–15}

In the few studies reporting antituberculous medication leading to DRESS, HHV-7 had not been tested.^{13–15} To our knowledge, our case is the first to detect HHV-7 DNA in a definite DRESS case after anti-TB drugs administration.

Learning points

- ▶ Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe adverse reaction with a high mortality rate.
- ▶ DRESS syndrome can be associated with other herpes viruses including human herpes virus 7.
- ▶ DRESS syndrome can occur due to antituberculous medication, and alternatives antituberculous regimen will need to be started.
- ▶ If medication causing DRESS is stopped promptly, there may be no role for steroids.

Acknowledgements The authors express their sincere thanks to Dr Tanzina Haque (Consultant virology, Senior lecturer Royal Free Hospital and UCL Medical School) for her advice on investigating the case and revising the manuscript.

Contributors All authors have made an individual contribution to the writing and have seen and approved the final version of the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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