CASE REPORT

Lamotrigine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) during primary Epstein-Barr virus (EBV) infection

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Accepted 3 January 2018

SUMMARY

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe, potentially life-threatening idiosyncratic drug reaction that may result in skin eruption, mucous membrane involvement, eosinophilia, atypical lymphocytosis and lymphadenopathy, with wide-ranging internal organ involvement. The authors report the case of a 21-year-old man who was prescribed lamotrigine for anxiety disorder. After 2 weeks of treatment, he developed a pruritic morbilliform rash on his trunk and upper extremities that was associated with fever, sore throat, bilateral scleral injection, nausea, vomiting and abdominal pain. A laboratory work-up revealed elevated transaminases and atypical lymphocytosis. He was found to have an active Epstein-Barr virus infection. Lamotrigine was discontinued due to suspicion of DRESS; the patient received pulsed intravenous methylprednisolone followed by oral prednisone taper, which resulted in a significant improvement of symptoms. At follow-up 3 weeks later, signs and symptoms had completely resolved. Follow-up laboratory tests revealed that liver dysfunction had normalised.

BACKGROUND

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare idiosyncratic drug reaction characterised by skin eruption, eosinophilia, atypical lymphocytosis, lymphadenopathy, and the involvement of internal organs such as the liver, lungs and kidneys. Mucous membrane involvement has also been reported. The initial event in this reaction is often viral reactivation; the virus in question is typically a member of the herpes family, such as human herpesvirus-6 (HHV-6), Epstein-Barr virus (EBV) or cytomegalovirus.^{1–3} In contrast, DRESS is rarely reported in patients during primary viral infection. Indeed, only five patients to date have been reported to have DRESS during primary EBV infection.^{4–8} Here, we report a case of DRESS induced by lamotrigine during primary EBV infection.

CASE PRESENTATION

A 21-year-old man with a history of generalised anxiety disorder was admitted to our hospital for a skin rash involving his trunk and upper extremities that developed over 3 days and was associated with high-grade fever, sore throat, scleral injection, periorbital swelling, nausea, vomiting and abdominal

pain. He had begun lamotrigine treatment for anxiety disorder approximately 2 weeks earlier.

His body temperature was 40.3°C, and he had a pruritic morbilliform rash on his trunk and upper extremities with bilateral scleral injections. No oral lesion, periorbital swelling, lymphadenopathy, hepatomegaly or splenomegaly was observed.

INVESTIGATIONS

Complete blood counts revealed a leucocyte count of $4.89 \times 10^9/L$ with 10% atypical lymphocytes, a haemoglobin concentration of 15.9 g/dL and a platelet count of $79 \text{ k}/\mu\text{L}$. Blood chemistry indicated that aspartate aminotransferase was 390 U/L, alanine aminotransferase was 506 U/L and alkaline phosphatase was 246 U/L. Lactate was 10.3 mmol/L. The Monospot test, a test for heterophile antibodies, which are usually present in active EBV infection, was positive. The patient was positive for EBV capsid antigen IgM antibodies and negative for EBV capsid antigen IgG antibodies; these findings are indicative of primary EBV infection. A punch biopsy of skin lesions revealed a combination of spongiotic and interfacial changes with numerous eosinophils, suggesting a drug reaction.

TREATMENT

Lamotrigine was discontinued, and the patient received pulsed intravenous methylprednisolone 125 mg once daily for 3 days; clinical improvement was observed. He was discharged on an oral prednisone 60 mg once daily, which was tapered over 3 weeks.

OUTCOME AND FOLLOW-UP

At follow-up 3 weeks later, signs and symptoms had resolved, and the abnormal laboratory test results described above had normalised.

DISCUSSION

DRESS is a drug-induced hypersensitivity reaction with manifestations such as skin eruption, fever, malaise, lymphadenopathy, eosinophilia, atypical lymphocytosis and the involvement of multiple organs (the liver, kidneys and lungs). DRESS typically develops 2–8 weeks after drug exposure and is frequently associated with reactivation of a latent herpesvirus infection.^{1–3}

Drug-specific immune responses and herpesvirus reactivation are two important factors in the

To cite: Tawhari I, Tawhari F, Aljuaid M. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222416

pathogenesis of DRESS. However, the development of DRESS during primary EBV infection is a rare phenomenon that has previously been reported in only five cases.^{4–8} Picard *et al* prospectively assessed 40 patients who exhibited DRESS and found reactivation of EBV, HHV-6 or HHV-7 in most of these patients. In all patients, elevation of activated CD8+ T lymphocytes, which are largely directed against herpesviruses such as EBV, was responsible for the cutaneous and visceral manifestations of EBV.⁹

In the RegiSCAR study, which involved a multinational registry of severe cutaneous adverse reactions, 201 potential cases were prospectively enrolled from 2003 to mid-2009 to analyse the spectrum of signs and symptoms of DRESS and the distribution of causative agents. A standardised scoring system was employed to validate 117 cases as apparent or probable DRESS. Antiepileptic agents (such as phenytoin, carbamazepine and phenobarbital) and allopurinol were found to be the most frequently reported inducing agents.¹⁰

There are no guidelines regarding the treatment of DRESS, and discontinuation of the culprit agent remains the mainstay treatment for DRESS. Systemic steroids have been used in the management of DRESS, and good outcomes of this approach have been described in individual case reports. Relapses have occurred after the withdrawal or tapering of steroids; such relapses also suggest the important role of steroids in the treatment of DRESS. However, no available randomised controlled trials have demonstrated the effects of steroids on DRESS.

Learning points

- ▶ Drug reaction with eosinophilia and systemic symptoms (DRESS) can be life-threatening, and early diagnosis and discontinuation of the offending medication are necessary.
- ▶ Viral reactivation is an important factor in DRESS pathogenesis. However, DRESS can also develop during primary viral infection.
- ▶ Systemic steroid use in the management of DRESS has been associated with good outcomes, especially in the setting of internal organ involvement.

Moreover, dosages, routes, durations and indications for systemic steroids have not been clearly defined.¹¹

Contributors IT was involved in the initial assessment, management and follow-up of the patient, and contributed towards the writing of this case report. FT identified the previously reported cases in the literature. MA participated in the literature review and was also involved in the management of the patient. All authors reviewed the final manuscript and approved it.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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