



Letter

Drug reaction with eosinophilia and systemic symptoms and cytomegalovirus colitis

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a multisystem delayed hypersensitivity reaction. Drugs most frequently implicated include anticonvulsants, allopurinol, and antibiotics. Typical manifestations include rash, fevers, lymphadenopathy, eosinophilia, and reactive lymphocytosis. Internal organ involvement frequently occurs, most commonly involving the liver, kidneys, lungs, and heart.¹ Gastrointestinal involvement is uncommon, occurring in approximately 5% of cases.¹

Reactivation of latent herpesviruses, such as human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and cytomegalovirus (CMV), is implicated in DRESS pathogenesis and is associated with a more protracted and severe disease course.² There are reports of herpesvirus reactivation causing organ specific disease, sometimes proving fatal. We report a case of DRESS associated with CMV reactivation causing colitis, the first with a confirmatory tissue biopsy.

A 77-year old man with hypertension and idiopathic peripheral neuropathy was administered intravenous vancomycin for empiric management of culture-negative left knee prosthetic joint infection. Twenty days after commencing treatment with vancomycin, he developed a generalized erythematous maculopapular rash. A week later he developed profuse diarrhea.

Vancomycin treatment was ceased on day 8 after onset of rash. Despite this, the patient was admitted to the hospital 2 days later for ongoing rash, diarrhea, and malaise. Investigations revealed acute kidney injury (serum creatinine, 389 $\mu\text{mol/L}$) and peripheral eosinophilia (eosinophils, $3.55 \times 10^9/\text{L}$). Blood film showed reactive lymphocytes. Liver function test results were unremarkable and remained so. Multiple stool specimens tested negative for infection. A skin biopsy specimen showed lichenoid interface dermatitis with perivascular and interstitial eosinophils and focal neutrophil spongiosis. A diagnosis of DRESS secondary to vancomycin (Registry of Severe Cutaneous Adverse Reaction score of 6) was made. Antibiotic therapy was ceased, and topical corticosteroids commenced.

During the next 5 days the patient developed fevers and had a progressive increase in eosinophilia and deterioration of renal function with eosinophiluria. He became anuric and required hemodialysis. A renal biopsy confirmed acute interstitial nephritis. Treatment with prednisolone, 50 mg/d, was commenced.

The results of initial investigations for herpesvirus reactivation were negative, with undetectable HHV-6, EBV, and CMV by polymerase chain reaction (PCR) on day 13 after onset of rash. CMV serologic findings were consistent with past infection (detectable CMV IgG, undetectable CMV IgM). After commencement of

treatment with prednisolone, the rash, eosinophilia, and renal function improved. However, diarrhea continued.

Sigmoidoscopy was performed (day 38) and revealed pancolitis. Biopsy specimens showed acute colitis with a mixed inflammatory infiltrate and presence of inclusion bodies, and immunohistochemistry studies confirmed CMV colitis (Fig 1). A subsequent peripheral blood CMV PCR revealed an elevated viral load at a level of 162,223 copies/mL (day 42). HHV-6 and EBV PCR results remained negative.

The patient thus commenced intravenous ganciclovir for management of CMV colitis (day 42). The diarrhea subsequently improved. Ganciclovir treatment was ceased once the viral load was undetectable 18 days later, and oral valganciclovir treatment was continued for an additional 2 months. After this, the patient had several relapses of rash and eosinophilia, although without evidence of CMV reactivation or other internal organ involvement. Prednisolone therapy was weaned gradually during the next 9 months. The case was further complicated by multiple bacterial infections and deep vein thrombosis.

Although it is recognized that DRESS can uncommonly involve the gastrointestinal tract,¹ and there are reports of DRESS manifesting with enterocolitis specifically, the clinical and histopathologic findings in these cases are heterogeneous.³ This finding suggests multiple pathologic processes through which DRESS can involve the gastrointestinal tract.

Cases of DRESS with both CMV reactivation and gastrointestinal tract involvement have been reported,^{2,4} but in most cases a confirmatory biopsy (the gold standard for diagnosis of CMV tissue invasive disease) appears not to have been performed; instead, the diagnosis was presumably based on the presence of compatible symptoms in association with elevated viral loads on peripheral blood CMV PCR.

Although detection of CMV viremia with PCR is widely used for diagnosis and monitoring of active CMV, a negative result does not exclude the diagnosis. One study investigating CMV gastrointestinal disease in patients undergoing solid organ transplant found that the sensitivity of peripheral blood PCR was 85%.⁵ Within their cohort were 3 patients with biopsy-proven CMV gastrointestinal disease with negative CMV PCR results.⁵ Therefore, it is important to consider targeted tissue biopsy if there is strong clinical suspicion despite negative PCR results. To our knowledge, ours is the first peer-reviewed case of DRESS with tissue-confirmed CMV colitis because the only other published report is an abstract.⁶

Herpesvirus reactivation in DRESS occurs stepwise. HHV-6 and EBV appear first, typically within 2 to 3 weeks of symptom onset, followed by HHV-7 and CMV 10 to 21 days later.⁷ This finding may explain why the results of the initial CMV PCR performed on day 13 in our patient were negative. However, if we accept that our

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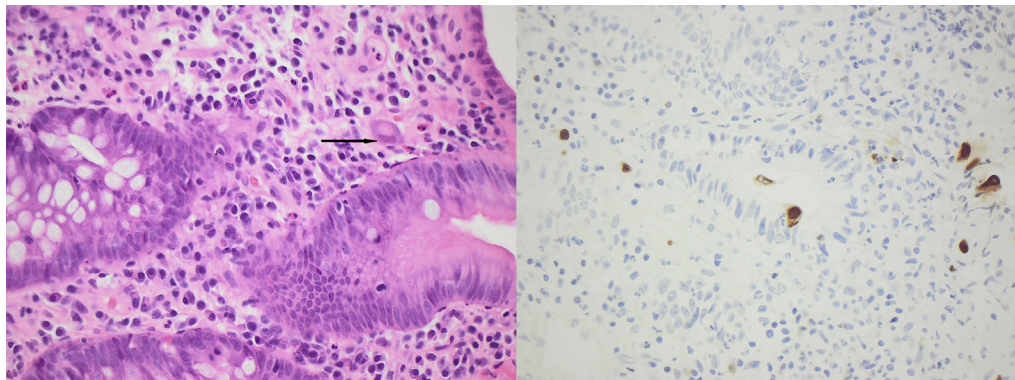


Figure 1. Cytomegalovirus colitis. Left, Enlarged mesenchymal cell in the lamina propria with a magenta-colored cytomegalovirus inclusion (arrow). Right, Cytomegalovirus immunohistochemistry. H&E, magnification $\times 400$

patient's diarrhea, which started on day 7, was caused by CMV colitis, then CMV may have been reactivated in tissue sooner than expected. Could there be a period wherein CMV has reactivated in tissue but has not yet progressed to detectable viremia? Patients with DRESS are typically not as immunocompromised as solid organ transplant recipients, from whom much of the knowledge regarding kinetics of CMV reactivation has been gathered; the progression from tissue reactivation to viremia perhaps differs in DRESS.

Herpesvirus reactivation in DRESS does not typically require antiviral therapy. However, in our case, although rash and eosinophilia improved with systemic corticosteroids, the diarrhea continued. It was not until commencement of specific antiviral therapy with ganciclovir that this improved. In DRESS, herpesvirus reactivation, particularly CMV reactivation, is associated with a more protracted course, increased complications, and higher mortality rates.² CMV reactivation may be predicted early via a scoring system.²

Given that high-dose corticosteroids may exacerbate infectious complications, thorough evaluation for viral reactivation, including targeted biopsy, should be considered before their introduction. Further research is required to clarify indications for antiviral therapy in DRESS and to establish how viral reactivation should be optimally monitored.

In conclusion, we present the first case, to our knowledge, of DRESS with biopsy-confirmed CMV colitis. There should be a high index of suspicion for CMV reactivation in DRESS, which can manifest in an organ-specific manner and can be missed on routine peripheral blood monitoring. Targeted tissue biopsy may facilitate an earlier diagnosis. Prompt institution of antiviral therapy can improve prognosis.

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