

Virus Reactivation in Drug Reaction with Eosinophilia and Systemic Symptoms (Dress) Results from a Strong Drug-Specific Immune Response



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The readers of *The Journal of Allergy and Clinical Immunology: In Practice* are certainly familiar with the acronym DRESS (drug reaction with eosinophilia and systemic symptoms), also called DiHS by Japanese authors for drug-induced hypersensitivity syndrome. Both acronyms delineate a specific clinical and biological phenotype of severe adverse drug reactions (ADRs) observed after exposure to a limited number of “high risk” medications.

VIRUS REACTIVATION IS AN ORIGINAL FEATURE OF DRESS

Many investigators have reported that DRESS was accompanied by reactivation of one or several viruses of the herpes group, including human herpesvirus 6 (HHV6), HHV7, Epstein Barr virus (EBV), and human cytomegalovirus,^{1,2} with a peak 2 to 3 weeks after initial symptoms.¹ Virus reactivation has been reported in up to 60% of patients with DRESS,² but it is neither invariable nor specific for DRESS, because viral activation has also been observed, even if less frequently, in other severe reactions such as Steven-Johnson syndrome and toxic epidermal necrolysis.¹ Recently the concept has even been proposed that DRESS is “no more than a viral disease” triggered by a direct effect (pharmacologic?) of medications on virus reactivation.³

Reports on virus reactivation in DRESS suffer from some important limitations. To date, we found no evidence of the presence of complete infective viral particles or encapsidated viral DNA sequences in the blood, plasma, and/or tissues from patients with DRESS. The prevalence of virus reactivation has been probably overestimated by the use of a technique that is too sensitive (quantitative real-time polymerase chain reaction on

plasma).⁴ Nonetheless, given concordant reports from so many teams from different countries, virus reactivation in DRESS can be accepted as a fact. That is especially supported by the finding of EBV-specific CD8 T cells in tissues from patients with DRESS,⁵ a classic marker of a normal immune response after EBV reactivation.

Viral reactivations are known to induce severe complications in immunocompromised patients especially in the setting of organ or bone marrow transplantation and in AIDS. Conversely, in immune-competent adults, such reactivations are most often asymptomatic according to virology textbooks.

STRONG DRUG-SPECIFIC IMMUNE RESPONSE IS ANOTHER ORIGINAL FEATURE OF DRESS

In the current issue of *JACI: In Practice*, Hensel et al⁶ describe the immunopathologic features of a positive patch test to ceftriaxone in a case of DRESS, with a similar pattern to that of a prior biopsy of the rash, and suggesting a mixed type IVb and IVc hypersensitivity. Too few similar reports of patch test biopsies are available in DRESS, and more would be welcome.

If not definitely conclusive on immunological mechanisms of DRESS, the demonstration of positive patch tests to drugs is a very strong challenge to the viral theory. Who can imagine a local viral reactivation followed by a local antiviral immune response within the 2 to 3 days between application and reading of the patch test?

Rates of positive patch tests to medications are actually much higher in DRESS (64% of cases) than in other severe cutaneous ADRs, and positivity of patch tests can be detected as long as 11 years after DRESS.⁷ Patch tests may even induce a relapse of a generalized rash.⁸ *In vitro* lymphocyte activation tests are also more frequently positive and exhibit a stronger response in DRESS than in other cutaneous ADRs.^{9,10} One half of DRESS relapses reported after accidental oral readministration of causative drugs developed within 3 days.¹¹ Each of the above findings clearly points to a strong and long-lasting drug-specific immunological memory in DRESS.

WHAT IS THE MOST LIKELY PRIMARY EVENT IN DRESS: VIRUS ACTIVATION OR DRUG ALLERGY?

There is no credible explanation of how virus reactivation, peaking 2 to 3 weeks after onset of DRESS,¹ could induce a drug-specific immune response. Supporters of the viral theory of DRESS often refer both to the high frequency of eruptions due to aminopenicillins observed during EBV primary infection (infectious mononucleosis) and to the high rates of ADRs in persons living with human immunodeficiency virus (HIV).

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However, the incidence of amoxicillin-induced rash in pediatric patients with EBV primary infection is actually much lower than previously reported, and the frequent positivity of patch tests has confirmed that the rash is secondary to sensitization to aminopenicillins.¹² The present figures of rash incidence in EBV infection with antibiotics remain higher (up to 33%) than in pediatric cases of infectious mononucleosis without antibiotics (23%), but this incidence may be still overestimated because of a likely referral bias, that is, an increased probability of diagnosis of infectious mononucleosis and hospitalization in case of rash.

In a prospective comparative study of patients with AIDS, the risk of sulfonamide-associated rashes was associated with alterations of immune response but not to any marker of viral replication for HIV, EBV, CMV, HHV6, and parvovirus B19.¹³ On the other hand, the capacity of stimulated lymphocytes to reactivate and release viruses is well established. Decades ago the knowledge that lymphocytes in charge of the “cellular response” released viral particles on nonspecific (mitogens) or specific (antigens) stimulation was the rationale for a “virus plaque assay” enumerating immunologically activated cells.¹⁴ The plaque assay used the release by activated lymphocytes of a cytolytic virus (vesicular stomatitis virus [VSV]) to count, as the number of activated T cells, the “holes” (plaques) observed on a layer of VSV-sensitive cells. Release of viruses by activated T cells was not only restricted to VSV, an RNA virus, but also observed for DNA viruses such as HSV, EBV, HHV7, and HHV6.¹⁵ Latent HHV6 reactivation was obtained after the cells were infected with HHV7, a finding that may explain the “cascade of herpesvirus reactivation” in DRESS.

Other classical inducers of reactivation of viruses in latently infected cells are short- and medium-chain fatty acids¹⁶ including valproic acid (VPA), prescribed in clinical practice as an anticonvulsant. Using the example of VPA to support the contention that medications can induce virus activation³ is questionable because VPA is the anticonvulsant with the lowest risk of hypersensitivity to the point of being recommended as first-line alternative treatment after a reaction to another antiepileptic agent.

Taken altogether, the above data strongly support the hypothesis that virus reactivation in DRESS is most likely secondary to a strong drug-specific immune response. That would be consistent with the occurrence of HHV6 reactivation in the patient with the positive drug patch test presented in the current issue of *JACI: In Practice*.⁶ Nonetheless, that does not answer the most important clinical question of whether or not virus reactivation in DRESS is harmful. Detection of EBV-specific CD8 T cells in the liver, skin, and lung of patients with DRESS⁵ is not proof of pathogenicity because virus reactivation is expected to be asymptomatic in normal adults, precisely because of a virus-specific immune response. However, in patients strongly immunocompromised by cancer chemotherapy, viral reactivation, especially of CMV, can be the source of severe potentially life-threatening complications.

Concerning DRESS, we found only 2 studies directly addressing the question of the clinical impact of virus reactivation by comparing cases with and without reactivation.^{2,17} Both included a limited number of patients. The first reported that fever, lymph node enlargement, atypical lymphocytes, hepatitis, and prolonged evolution of disease were significantly more frequent with virus reactivation (defined only as a rise in anti-HHV6 antibodies).² The second study¹⁷ found more elevated fever, flares, and disease

duration in 10 patients with virus activation compared with 13 without. Neither of these series tried to control for the likely most important factor: the strength of the drug-specific immune response, expected to be the source of viral reactivation and the essential factor determining severity.

At the present time we consider that a specific contribution of virus reactivation to DRESS symptoms and severity is possible but not yet established. Larger studies are needed comparing DRESS cases with and without virus reactivation, and taking in account the strength of drug-specific response. Awaiting a better evaluation of the clinical consequences of virus reactivation in DRESS, there are many arguments suggesting that drug is necessary for DRESS development while virus is not.

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