Drug-induced severe adverse reaction enhanced by human herpes virus-6 reactivation

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Reactivation of certain latent viruses has been linked with a more severe course of drug-induced hypersensitivity reaction (HSR). For example, reactivation of human herpes virus (HHV)-6 is associated with severe organ involvement and a prolonged course of disease. The present study discusses an HSR developed in a previously healthy male exposed to ceftriaxone, doxycycline, vancomycin, and trimethoprim/sulfamethoxazole (co-trimoxazole; TMP/SMX). Initially, the patient presented clinical manifestations of HSR, as well as clinical and laboratory measurements compatible with liver and renal failure. Moreover, the patient presented skin desquamation compatible with Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis. During the reaction, it was observed HHV-6 reactivation. The severity of clinical symptoms is correlated with HHV-6 titer, as well as with results of the *in vitro* lymphocyte toxicity assay (LTA). Serum levels of a large panel of cytokines are compared between the patient, a large population of SJS patients, and a cohort of healthy controls, using data collected by our laboratory over the years. HHV-6 was measured in the cell culture media from lymphocytes incubated with each of the 4 drugs. Moreover, we describe a new assay using cytokines released by patient lymphocytes following *in vitro* exposure to the incriminated drugs as biomarkers of HSR. Based on LTA results, HHV-6 reactivation and cytokine measurements, we establish that only doxycycline and TMP/SMX were involved in the HSR. As result of this analysis, the patient could continue to use the other 2 antibiotics safely. (Translational Research 2013;161:430–440)

Abbreviations: ADR = adverse drug reaction; DIHS = drug-induced hypersensitivity syndrome; DILI = drug-induced liver injury; DRESS = drug reaction with eosinophilia and systemic symptoms; HCMV = human cytomegalovirus; HHV = human herpes virus; HSR = hypersensitivity reactions; IFN = interferon; IL = interleukin; LTA = lymphocyte toxicity assay; MCP = monocyte chemoattractant protein; NF = nuclear factor; PCR = polymerase chain reaction; RANTES = regulated upon activation normal T-cell expressed and secreted; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; TMP/SMX = trimethoprim/sulfamethoxazole; TNF = tumor necrosis factor

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AT A GLANCE COMMENTARY

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In this case a young individual was given 4 different antibiotics to prevent an infection. As a result he developed an idiosyncratic reaction that was diagnosed by the physician initially as DRESS. The manifestation was followed by liver damage (DILI) and by epidermal detachment compatible with Stevens-Johnson syndrome (SJS). This is an original investigation bringing biomedical research from clinical and laboratory medicine. Aiming to expedite the translation of lymphocyte toxicity assay as a diagnostic tool into improved standards of drug-induced toxicity care, this article promotes an exchange between preclinical and clinical outcomes.

This article presents a comprehensive example of interdisciplinary, interactive translational research. In it, we described the dynamic of a clinical case. The laboratory work contributed to the elucidation of several aspects of this case that involved clinical investigation as well as pharmacologic, immunologic, and viral determinations. The clinician has adopted the results of the lymphocyte toxicity assay, which indicated that two of the four antibiotics administered to the said patient were toxic. Also, this article describes the importance of a latent virus human herpes virus-6 (HHV-6) reactivation in SJS. As a result of the teamwork involving one clinician and laboratory medicine specialists in clinical chemistry, clinical pharmacology, and clinical virology, the patient was treated safely and recovered from his injuries.

A variety of chemical agents can induce hepatic or skin injury leading to adverse events.[1] According to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, an adverse drug reactions (ADR) is defined as a noxious and unintended reaction to a drug that occurs at doses normally used in humans for prophylaxis, diagnosis or treatment of disease, or for the modification of physiologic function.[2] ADRs are recognized as the cause of over 5% of total hospital admissions, whereas a higher incidence of over 15% is observed among hospitalized patients.[3,4] A similar incidence was observed in a multinational hospital pediatric sample.[5] Over 2000 different pharmaceutical agents have been associated with ADRs in 8 European electronic healthcare databases.[6] At the same time, multiple drug exposure is recognized as a risk factor for developing ADRs.[7]

Idiosyncratic type B ADRs account for about 15%–20% of these reactions.[3,8] Hypersensitivity reactions (HSR) are unpredictable host-dependent ADRs that can occur independent of the dose, frequency or length of the treatment, and cannot be anticipated by animal models. A "true" HSR is comprised of the triad of fever, rash and internal organ involvement.[1,9-18]

The incidence of HSRs ranges from 1 in 1000 to 1 in 10,000 drug exposures, with approximately 10% of these cases being lethal.[14,17,19] The clinical presentation of HSR can include cutaneous involvement such as morbilliform rash, urticaria, angioedema, fever, malaise, anaphylaxis, bronchospasm, and erythema multiforme. The more complex cases of HSR are associated with severe cutaneous adverse reactions such as drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN).[9,11,13-15,17-22]

The internal organ most often affected is the liver, with drug-induced liver injury (DILI) ranging from elevations in liver function tests and hepatomegaly, to liver failure requiring organ transplantation.[15,18,19] Serum bilirubin levels raised >3 times over the upper limit of normal in the presence of aminotransferase elevations is associated with a more severe set of symptoms compared with isolated aminotransferase abnormalities alone, an observation known as Hy's Law.[23] DILI characteristics can be further subdivided into several categories. Some agents lead to necrosis, steatosis, cirrhosis, or carcinoma, whereas others lead only to interference with bile secretion and to jaundice, with little or no overt injury to the hepatic parenchyma. Some produce vascular lesions. Indeed, drugs can produce the entire range of known hepatic lesions.[24-27]

The highest incidence of HSRs has been reported following exposure to anticonvulsants.[28-34] Other classes of drugs such as allopurinol, nonsteroidal anti-inflammatory drugs, chlormezanone, aminopenicillins, cephalosporins, quinolones cycline antibiotics, antiretrovirals, as well as sulfonamide antibiotics have been implicated as well.[13-15,17,19,21,22,35-38] Hypersensitive individuals are believed to carry defects in drug detoxifying pathways.[9,11,17] Immune responses can also play a role in HSR development through secretion of high levels of proinflammatory cytokines and chemokines.[14,18,39]

Reactivation of certain latent viruses has been linked with a more severe course of disease. For example, reactivation of human herpes virus (HHV)-6 is associated with more severe organ involvement and a prolonged course of disease, particularly among DIHS patients.[40,41] Close to 100% of individuals are thought to