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High Level Human Herpesvirus-6 Viremia Associated with onset of Stevens-Johnson Syndrome: Report of 2 Cases

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Abstract

The pathogenesis of Stevens Johnson Syndrome (SJS) remains obscure but it has been associated with various infectious agents, including members of the Herpes virus family. We present the first report of high level human herpesvirus-6 (HHV-6) viremia at the onset of SJS suggesting a possible new association. This finding supports the need for further investigation into the possible relationship between HHV-6 and SJS which may illuminate the pathogenesis of SJS and bring us closer to achieving enhanced prevention and treatment of this rare disease.

Keywords

Human Herpesvirus-6; HHV-6; Stevens-Johnson Syndrome; Herpes Viruses

Introduction

Stevens-Johnson Syndrome (SJS) is a rare, idiopathic and poorly understood immunologically mediated muco-cutaneous process that is part of a continuum with bullous Erythema Multiforme (EM) and Toxic Epidermal Necrolysis Syndrome (TEN)(1) although EM remains somewhat distinct from SJS/TENS based on a much stronger association with infectious inciting agents. The pathogenesis of SJS is thought to be initiated by an immune

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response to an antigenic complex formed by drug metabolites or microorganisms. Genetic susceptibility has also been implicated with an increased incidence in persons with the HLA-B12 allele (2). It has been associated with numerous drugs and infectious agents, including members of the Herpes virus family such as herpes simplex virus (HSV), cytomegalovirus (CMV) and varicella-zoster virus (VZV) (3-6). Erythema multiforme is strongly associated with HSV types I and II, with HSV encoded proteins identified in affected epidermis and HSV DNA detected in target lesions (7-9).

Human herpesvirus 6 (HHV-6) was first identified in 1986 and quickly reported as the etiology of childhood roseola infantum (Sixth disease, exanthum subitum) (10-14). Like other herpes viruses, HHV-6 remains latent in host cells after primary infection but can reactivate when the immune system is suppressed. In recent years HHV-6 has been recognized as an emerging pathogen associated with pneumonitis and encephalitis following stem-cell transplantation (15-17) and may be associated with drug-induced hypersensitivity syndrome (18). Other novel associations continue to be explored (19-21). In this report, we describe two immunocompetent patients with SJS associated with high level HHV-6 variant B viremia at onset of clinical presentation. Given its ubiquitous nature, HHV-6 may account for a proportion of idiopathic cases of SJS.

Case 1

An 18-year old female with a history of recurrent oral and genital HSV outbreaks presented with fever, malaise and myalgias, and subsequently developed 60% total body surface area involvement with target lesions, extensive erythematous plaques, bullae involving her face, neck, arms, chest, abdomen and proximal extremities as well as epithelial defects and pseudomembrane involvement of both conjunctivae. She had extensive orolabial and genital mucosal surface denudement and complete epidermal detachment of at least 10% of the skin surface of her chest, abdomen, back and face consistent with SJS/TENS (Toxic Epidermal Necrolysis Syndrome) based on standard classification (1). Her long-standing medications included valacyclovir, promethazine, synthroid, belladonna and orthotricycline. She had not taken any newly prescribed medications. Skin biopsy demonstrated vacuolar interface dermatitis with a few apoptotic keratinocytes and focal sub-epidermal cleft formation consistent with erythema multiforme or early Stevens-Johnson Syndrome. There was no viral cytopathic effect noted. Corticosteroids were not administered.

Diagnostic studies included negative urine, blood, and genital tract bacterial cultures, anti-streptococcal antibodies, *Mycoplasma* serologies, HIV ELISA and PCR, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) plasma PCR tests, and monospot test. HSV type 1 and 2 PCR tests from genital tract and inner thigh erosion samples were negative. However, HHV-6 plasma PCR showed high-level viremia (ViraCor laboratories) 115,000 DNA copies/mL (plasma sample obtained prior to first IVIG administration). Genotyping by real-time PCR identified HHV-6 variant B. Initial serologies (obtained after the initiation of intravenous immunoglobulin) showed an IgG of 1:320 and IgM <1:20 (Focus Diagnostics). Repeat serologies at 4 weeks reported IgG 1:640 and IgM<1:20. Surprisingly, she continued to be viremic at weeks 2, 4 and 8 with values of 19,100 copies/mL, 18,300 copies/mL and 20,400 copies/mL respectively. At week 14, HHV-6 level had dropped to 2,700 DNA

copies/mL and IgG was 1:10 and IgM<1:20. Sequential EBV and CMV plasma DNA PCR testing remained negative.

Case 2

A 64-year old woman presented with five days of progressive sore throat, eye irritation and malaise and developed target lesions on a background of symmetric diffuse (approximately 80% total body surface area) erythematous papules and confluent erythema that progressed to extensive epidermal detachment (approximately 50% body surface area) as well as mucosal erosions involving her conjunctiva and oropharynx. Punch biopsy confirmed vacuolar interface and sub-epidermal vesicular dermatitis with focal full thickness epidermal necrosis consistent with SJS (see figure). Approximately one month prior to this she was treated for a flare of gout with a two-week course of prednisone and allopurinol, a drug associated with SJS/TEN. Long-standing medications included hydrochlorothiazide, dehydroepiandrosterone, glucosamine, aspirin, and ezetimibe/simvastatin. Corticosteroids and intravenous immunoglobulin were not administered.

Initial diagnostic evaluation included negative blood and urine cultures, rapid influenza A/B antigen detection, rapid group A *Streptococcus* antigen detection, anti-streptococcal antibodies, EBV and CMV plasma PCR tests. Initial HHV-6 qualitative plasma PCR was negative on hospital day #2 in the setting of extensive fluid resuscitation due to insensible losses and hypotension, however quantitative testing on hospital day #6 demonstrated 1,500 DNA copies/mL and by day #8 was 131,000 DNA copies/mL. Follow up HHV-6 viral load on hospital day #21 was 400 copies/mL. A lip erosion tested negative for HSV 1/2 by PCR, but tested positive for HHV-6 by PCR. Genotype testing confirmed HHV-6 variant B. Initial serologies showed HHV-6 IgG 1:640 and IgM <1:20. Convalescent serologies confirmed HHV-6 IgG 1:1280 and IgM <1:20. Sequential EBV and CMV plasma PCR tests remained negative.

In both patients, baseline serology testing for EBV and CMV were consistent with previous exposure and latency (+EBV viral capsid IgG, +CMV IgG) yet serial plasma PCR testing for reactivation of these other herpes viruses remained negative. The decision was made to withhold anti-viral therapy targeted at HHV-6 based on the unclear significance of this association and concern about added medication toxicity. Both patients survived but with substantial morbidity. In Case #1, the patient suffered corneal scarring with permanent blindness, oropharyngeal stricture and vaginolabial fusion; in Case #2, the patient had a prolonged hospitalization complicated by pseudomembranous conjunctivitis, pseudomonal pneumonia and multi-system organ failure. She was discharged with tracheostomy and feeding tube in place and continues to require hemodialysis.

Discussion

The ability of herpes viruses to lay dormant in host tissue following primary infection requires a functioning immune system to prevent reactivation. When there is a disruption or alteration in cell-mediated immunity, either because of the use of immunosuppressive agents, aging, alteration in cytokine expression (sepsis, burn injury, drug or allergic

reaction) or development of an immunosuppressive disorder (e.g., HIV/AIDS, malignancy), herpes viruses can replicate and cause an array of medical conditions (22). The relatively recent availability of nucleic acid amplification testing has identified many new conditions associated with herpes viruses.

In this report, we identified high level HHV-6 viremia temporally associated with the onset of SJS, a condition primarily associated with medications but also with herpes family viruses and other infectious agents. In Case #1, it is unclear if this represented primary or reactivated infection. The patient was younger, had no clear medication precipitant, and her HHV-6 viral load remained high for several weeks which may favor primary infection (serologies were confounded by the administration of IVIG; the IVIG administered to the patient was not tested for the presence of HHV-6 viral particles by PCR or culture, however standard manufacturing processes for IVIG incorporate rigorous viral elimination procedures [23]). However, reactivation still remains more likely based on sero-epidemiologic data supporting greater than 90% sero-prevalence of HHV-6 by the age of 2 (24). A third possibility is congenital chromosomally integrated HHV-6 which can occur in about 1% of the population and represents HHV-6 DNA fragments in every nucleated cell. While the decline in her viral load over time and the use of acellular (plasma) testing make this unlikely, specific testing for chromosomal integration using whole blood or hair follicles was not performed (25-26). In Case #2, serologic data supports reactivation disease. She had received allopurinol as well as a course of steroids prior to her illness which could have precipitated reactivation of HHV-6. Of interest, her lip erosion was positive for HHV-6 by PCR, however HHV-6 is commonly shed in saliva and could have contaminated the lesion. No viral cytopathic changes were visualized on skin biopsy in both cases but HHV-6 DNA/RNA testing and protein expression (gp116/54/64) by routine immunohistochemistry described by Fotheringham (27) was not performed. Approximately 10 subsequent patients with SJS/TEN at our institution, including pediatric patients (looking for an association with primary HHV-6 infection), have tested negative for HHV-6 viremia using the same diagnostic methods, suggesting HHV-6 as a rare etiology of SJS.

While these two patients presented with high level HHV-6 type B viremia, a causal role for HHV-6 in the development SJS cannot be explained without further investigation. Detection of HHV-6 viremia in non-immunocompromised patients with acute illness was described in one study of patients with multi-system organ failure in which 54% of patients had detectable serum HHV-6 DNA by polymerase chain reaction but quantification of viral load was not performed and HHV-6 genotype was not reported (28). A subsequent study of critically ill patients found a 53% rate of HHV-6 viremia at time of admission to an intensive care unit but the nucleic amplification technique utilized in that study included peripheral blood leukocytes which can be complicated by chromosomally integrated HHV-6 DNA (29). In that study, all but one case were typed as HHV-6 variant A (30). A recent report of low grade HHV-6 viremia in association with zonisamide related TEN also utilized whole blood testing which may be confounded by amplification of latent HHV-6 in peripheral monocytes, and in that case HHV-6 DNA was not found early in the disease course but was documented at day 22 of hospitalization. CMV and EBV reactivation were not reported to look for evidence of other herpes virus reactivation (31).

A possible role for HHV-6 in the pathogenesis of dermatologic conditions has previously been explored. In a study of drug induced hypersensitivity syndrome, Tohyama and colleagues showed that anti-HHV-6 IgG titers increased in 62% of patients and HHV-6 viremia was detected in 18% of patients (range 120-2,400,000 copies/mL) between 10-27 days after the onset of symptoms and was associated with more severe organ involvement, prolonged illness including flaring of fever and hepatitis, and mortality in comparison to those patients without evidence of HHV-6 reactivation (18). The authors postulate that potent drug-reactive T cells act similarly to alloreactive T cells following organ transplantation and may drive HHV-6 reactivation. Interestingly, they also report no cases of HHV-6 reactivation among 10 patients diagnosed with SJS or TEN in their discussion and a recent investigation in China into the etiology of SJS found no HHV-6 reactivation among 16 patients surveyed using DNA PCR (32). Therefore, we report the first two cases of SJS associated with high level HHV-6 viremia at onset of disease. Our report is limited based on data from 2 distinct patients, one of whom had allopurinol as a likely drug precipitant (case 2) and one of whom had IVIG administration (case 1) precluding conclusive serologic interpretation. However, the demonstration of high level viremia determined by quantitative real time PCR testing in the first week of hospitalization is compelling evidence for active HHV6 replication. Whether this replication is a bystander and marker of immune dysregulation or has a pathogenic role in these dermatologic conditions remains undefined but merits further investigation.

SJS is a serious and potentially lethal disease. There is currently no way to predict who may be affected and no means of prevention. Further research into the association of HHV-6 and SJS may illuminate its pathogenesis, help define the cascade of immunologic events induced by drug and viral antigens, and bring us closer to achieving enhanced prevention and treatment of this poorly understood disease.

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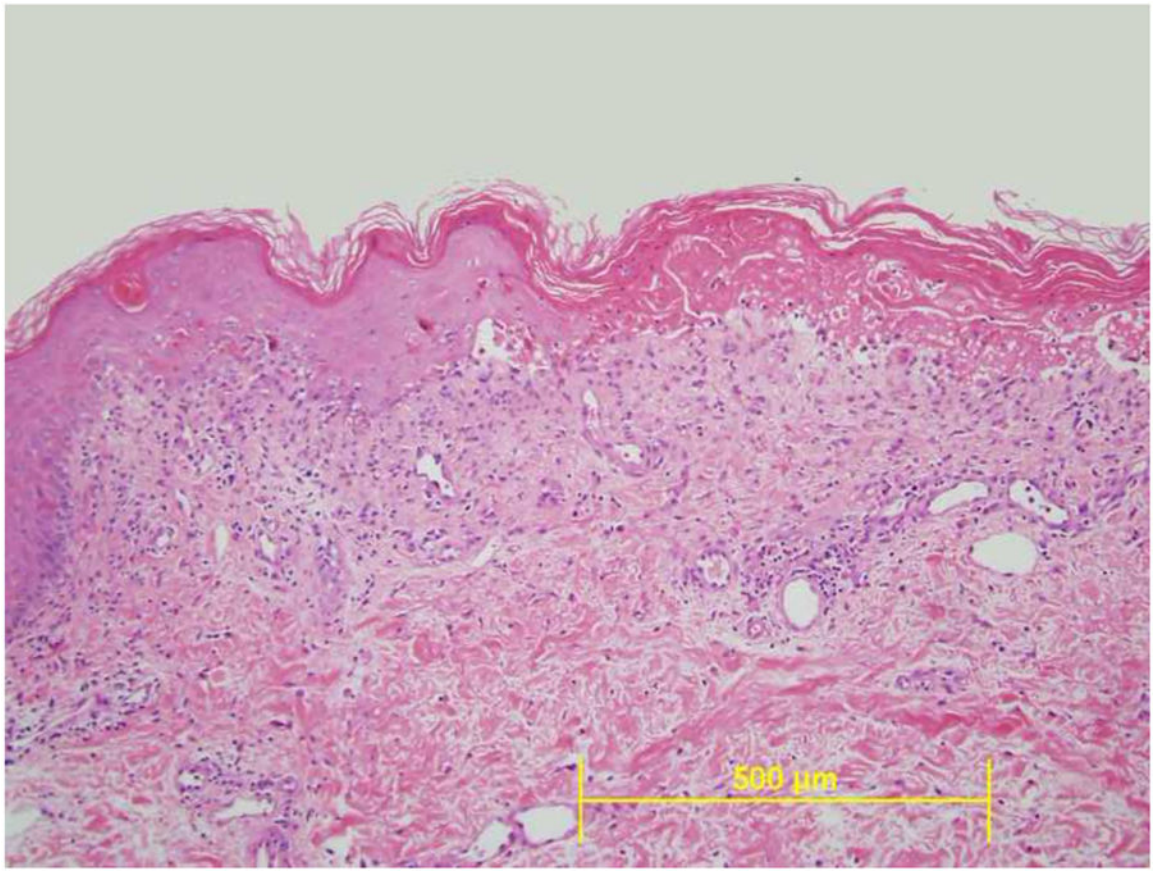

Figure.

Vacuolar alteration of the dermal epidermal interface associated with scattered apoptotic keratinocytes is present on the left side of the image with progression to subepidermal cleft formation and full thickness epidermal necrosis on the right side of the image (original magnification × 200).