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iciHHV-6 in a Patient With Multisystem Inflammatory Syndrome in Children (MIS-C)

Lisa Biswas[a], Noreen Crain[b], Michael C. Spaeder[b], Robert J. Gomez[c], Meghan Starolis[d], Melinda D. Poulter[e], Steven L. Zeichner[a,f]

Affiliations: [a]Department of Pediatrics, University of Virginia, Charlottesville, VA, USA; [b]Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Virginia, Charlottesville, VA, USA; [c]Division of Critical Care Medicine, Children's Hospital of the King's Daughters, Norfolk, VA, USA; [d]Quest Diagnostics Nichols Institute Chantilly, Chantilly, VA, USA, [e]Clinical Microbiology Laboratory. Department of Pathology, University of Virginia Health System, Charlottesville, VA, USA; [f]Department of Microbiology, Immunology, and Cancer Biology; Pendleton Pediatric Infectious Disease Laboratory; and Child Health Research Center, University of Virginia, Charlottesville, VA, USA

Address correspondence to: Steven L. Zeichner, Departments of Pediatrics and Microbiology, Immunology, and Cancer Biology; Pendleton Pediatric Infectious Disease Laboratory; and Child Health Research Center, University of Virginia, Charlottesville, VA 22908-0386, zeichner@virginia.edu, 434-297-7718

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Abbreviations: Coronavirus disease 2019: COVID-19, DRESS: drug rash with eosinophilia and systemic symptoms, HHV-6: Human Herpesvirus-6; iciHHV-6: inherited chromosomally integrated HHV-6; IL: interleukin, RBD: receptor binding domain, RT-PCR: reverse transcription polymerase chain reaction, SARS-CoV-2: severe acute respiratory syndrome coronavirus-2, S: SARS-CoV-2 spike protein, VL: viral load

Table of Contents Summary

We report an MIS-C case in a patient with iciHHV-6. Studies to determine whether chromosomally integrated HHV-6 is common in MIS-C patients may be warranted.

Contributors' Statement Page

Dr. Biswas drafted part of the initial manuscript, contributed to the analysis and interpretation of the data, and critically reviewed and revised the manuscript. Dr. Crain reviewed and revised the manuscript and contributed to the analysis and interpretation of the data. Dr. Spaeder reviewed and revised the manuscript contributed to the analysis and interpretation of the data. Dr. Gomez contributed initial clinical observations and reviewed the manuscript and contributed to the analysis and interpretation of the data. Dr. Starolis supervised certain laboratory testing, troubleshooting, confirmatory assays, and reviewed the manuscript and contributed to the analysis and interpretation of the data. Dr. Poulter reviewed and consulted on laboratory results and reviewed the manuscript and contributed to the analysis and interpretation of the data. Dr. Zeichner conceptualized the study, drafted part of the initial manuscript, and reviewed and revised the manuscript and contributed to the analysis and interpretation of the data. All authors helped to critically revise the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work and in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Multisystem inflammatory syndrome in children (MIS-C)is a serious, sometimes life-threatening late complication of COVID-19, with multiorgan involvement and evidence of immune activation. The pathogenesis of MIS-C is not known, nor is the pathogenesis of the severe organ damage that is the hallmark of MIS-C. HHV-6, the virus responsible for roseola, is a ubiquitous herpesvirus causing close to universal infection by the age of 3 years. HHV-6 remains latent for life and can be activated during inflammatory states, by other viruses, and by host cell apoptosis. HHV-6 has been associated with end organ diseases, including hepatitis, carditis, and encephalitis. In addition, ~1% of people have inherited chromosomally integrated (ici) HHV-6, which is HHV-6 that has been integrated into chromosomal telomeric regions that is transmitted through the germline. iciHHV-6 can be reactivated and has been associated with altered immune responses. We report here a case of MIS-C where an initial high HHV-6 DNA PCR viral load assay prompted testing for iciHHV-6, which was positive. Additional research may be warranted to determine whether iciHHV-6 is commonly observed in patients with MIS-C and, if so, whether it may play a part in MIS-C pathogenesis.

Multisystem inflammatory syndrome in children (MIS-C) is a severe hyperinflammatory process that is observed in a small number of children convalescing from COVID-19 [1-6]. The MIS-C case definition includes at least two of these features: rash, conjunctivitis, or mucocutaneous inflammation; hypotension; cardiac disease; coagulopathy; or acute gastrointestinal problems [7]. Some patients exhibit neurologic or neuropsychiatric symptoms with associated imaging abnormalities [8, 9]. MIS-C has several hyperinflammatory features. Patients can exhibit high levels of circulating proinflammatory cytokines (IL-6, IL-17A, and IL-18, interferon-gamma, and tumor necrosis factor-beta), and lymphocytes of MIS-C patients typically have increases in activation markers [10, 11]. Therapy for MIS-C includes corticosteroids and often includes monoclonal antibodies directed against proinflammatory cytokines and/or their receptors[10]. MIS-C typically appears days to a week or more after infection, often when SARS-CoV-2 viral loads (VL) have become undetectable [6]. The incidence of MIS-C is difficult to establish, since many children experience asymptomatic SARS-CoV-2 infection [5]. While there are many descriptions of the features of MIS-C, including important immunological associations[12], the detailed pathogenesis is not well established, although some reports have suggested an association between high levels of antibodies against the receptor binding domain (RBD) of the SARS-CoV-2 spike protein (S) and a higher risk for MIS-C [13-15]. Particular anti-SARS-CoV-2 antibody profiles and inflammatory marker and immune signatures have been associated with MIS-C [13, 16].

Human herpesvirus-6 (HHV-6), the causative agent of roseola (also known as sixth disease or exanthem subitem, syndromes that can also be caused by HHV-7 [17]), is a ubiquitous human pathogen (reviewed in [18-20]), with two strains, HHV-6A and HHV-6B [21]. HHV-6 infects almost all children in the first few years of life; infection is close to universal by age 3-4 years [22].

HHV-6 is also neurotropic, and primary HHV-6 infections can be associated with seizures and encephalitis. HHV-6 infects a variety of cell types, including B- and T- lymphocytes, monocytes, natural killer cells, dendritic cells, astrocytes, megakaryocytes, glial cells, and epithelial cells. As with other herpesviruses, HHV-6 can remain latent within an individual's cells throughout life [18, 20]. Primary disease due to HHV-6 is generally self-limited and is not typically treated, although several antiviral agents, including approved antiviral agents have activity against HHV-6 (reviewed in [23]). The cellular receptor for HHV-6A is CD46 [24], which is found on all nucleated cells , while the primary cellular receptor for HHV-6B is CD134 [25], a tumor necrosis factor superfamily member found on activated T-cells. HHV-6 can integrate into a cell's telomeric region, yielding inherited chromosomally integrated (ici) HHV-6, which can be transmitted in a Mendelian fashion (reviewed in [26-29]). The presence of iciHHV-6 has been associated with altered, and in some instances, increases in antibody responses to certain viruses [30], and has been associated with an increased risk of acute graft versus host disease and cytomegalovirus activation in hematopoietic cell transplant recipients [31, 32].

Antiviral agents approved for other indications with *in vitro* activity against HHV-6 and with reports of clinical response include cidofovir, ganciclovir and valganciclovir, and foscarnet, although the clinical utility of some agents can be problematic given their toxicity profiles [18]. An investigational cidofovir prodrug, brincidofovir, is under investigation for HHV-6 in hematopoietic cell transplant settings [33].

Both episomal and iciHHV-6 can be reactivated from latency (reviewed in [28]). HHV-6 reactivation and accompanying end organ disease affecting many systems has been observed in association with solid organ and bone marrow transplantation [20, 34]. High level HHV-6 reactivation has also been observed in association with drug rash with eosinophilia and systemic

symptoms (DRESS syndrome) [35, 36], which has been linked to elevated proinflammatory cytokines [36]. A study of the kinetics of proinflammatory cytokine production and HHV-6 activation in a small cohort of patients with drug induced hypersensitivity syndrome suggested that high levels of proinflammatory cytokines preceded HHV-6 activation, suggesting a possible causal link [37]. HHV-6 activation by proinflammatory cytokines may be difficult to establish directly, but has been often observed in the presence of HHV-7, which itself readily responds to inflammatory activation signals [38]. HHV-6 reactivation, particularly in transplant patients, can be associated with clinically significant disease, with features including fever, bone marrow suppression, interstitial pneumonitis, and encephalitis.

Here we report a case of MIS-C, initially found to have a high HHV-6 viral load, and then subsequently determined to have iciHHV-6.

In late December 2020, a 12-year-old male with obesity presented to an outside hospital emergency department after three days of headache, vomiting, and one day of altered mental status. He was febrile, hypotensive, and tachycardic upon presentation and ultimately transferred to their pediatric intensive care unit for worsening mental status. Because of the initial concern for sepsis, the patient received broad-spectrum antibiotics. Assays for multiple infectious agents, including viral pathogens that could help explain his altered mental status, were conducted. Several of these assays were sent to referral laboratories, which returned results after some time. The pathogen testing results are summarized in Table 1. An initial reverse transcription polymerase chain reaction (RT-PCR) based assay for SARS-CoV-2 was negative. The patient continued to have fevers as high as 40.8ºC despite receiving antibiotic and antipyretic treatment. Laboratory studies revealed elevated inflammatory markers, thrombocytopenia, coagulopathy, acute kidney injury, and transaminitis (Table 1). Elevation of troponin and brain natriuretic

peptide (BNP) was concerning for cardiac involvement (Table 1). An echocardiogram confirmed reduced cardiac function, with an initial ejection fraction of 44% that worsened to 25% on repeat echocardiogram, and the patient was placed on continuous vasoactive infusions to maintain adequate perfusion. He had severe cardiac dysfunction and acute respiratory failure requiring intubation. Given multi-system involvement, with increasing suspicion for MIS-C, he was treated with intravenous immunoglobulin (IVIG). Although the patient had no known history of COVID-19 infection or any other recent illnesses, COVID IgG serology, using a pre-IVIG serum sample, was obtained and found to be positive, confirming suspicion for MIS-C. He was transferred from the referring hospital to the University of Virginia (UVA) for further management.

At UVA, one repeat SARS-CoV-2 RT-PCR assay was positive at a very high cycle threshold value of 40 cycles, with a repeat SARS-CoV-2 RT-PCR that was negative. Following initiation of anakinra, an IL-1 inhibitor, and high dose methylprednisolone, he showed improvement in laboratory markers and clinical status. He was weaned from his vasopressor support, extubated to room air, and showed return of his end organ function. Antibiotics were discontinued after bacterial cultures remained negative. Viral pathogen testing sent by the referring hospital at the time of his initial admission returned negative for cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, herpes simplex virus, and parvovirus (Table 1). However, an HHV-6 PCR result, sent by the referring hospital, conducted by Quest Diagnostics Nichols Institute (Chantilly, VA) later revealed a high viral load of 1,123,094 viral DNA copies/mL (reference range <500 viral DNA copies/mL). The methodology used to determine the HHV-6 VL at the reference laboratory was reviewed, and it was determined that the test was conducted on a whole blood specimen, which raised the possibility that the high VL

resulted not from high level HHV-6 replication, but rather because the assay was detecting iciHHV-6 DNA from the patient's leucocytes. A sample of hair follicles was sent to Coppe Laboratories (Waukesha, WI), which tested the hair follicles for the U94 genes of HHV-6A and HHV-6B. HHV-6A was not detected, but HHV-6B was detected, indicating that the patient had iciHHV-6B. There were no other complications during his recovery.

To our knowledge, an association of MIS-C with iciHHV-6 has not been previously reported. Hyperinflammatory states similar to that seen in MIS-C are known to be associated with HHV-6 activation, including in patients with iciHHV-6. In addition, pro-apoptotic signals activate herpesviruses and retroviruses out of latency [39, 40]. The end organ dysfunction seen in MIS-C has substantial similarities to that seen in other hyperinflammatory states associated with HHV-6 activation [20, 34-36], so it is plausible that in some MIS-C patients, HHV-6 activation could contribute to the pathologies associated with MIS-C. This single case may prompt an interest in additional studies of HHV-6 in patients with MIS-C – either iciHHV-6 or activation of conventional episomally latent HHV-6. If HHV-6 is a common feature in MIS-C, that observation would constitute another contrast between MIS-C and Kawasaki disease, where high level HHV-6 activation has not been commonly observed.

Here we report a single case of iciHHV-6 in association with MIS-C. While no definitive conclusions can be drawn from a single case, it may be useful to study larger numbers of MIS-C patients to determine whether iciHHV-6 is commonly observed in association with MIS-C, particularly considering the observations that MIS-C patients can demonstrate enhanced antibody responses to SARS-CoV-2[13-15] and iciHHV-6 has been associated with increases in antibody responses to certain viruses [30]. Further study may reveal, in additional patients, an association between iciHHV-6 and MIS-C, or an additional association between the activation of

conventional HHV-6 and MIS-C, or no real further associations at all. Additional studies, however, may be warranted in efforts to better understand the pathogenesis of the disease. Currently available assays for iciHHV-6 require several days' turnaround time for results to become available, so iciHHV-6 assays in MIS-C patients would be considered in the context of a research study. If iciHHV-6 proved to be a common feature of MIS-C, it would be necessary to scale up and widely deploy the assay for it to be clinically useful. Although there are no FDA-approved antiviral agents for HHV-6, some agents have been employed off-label in patients with HHV-6-associated disorders [41, 42]. If iciHHV-6 is commonly associated with MIS-C, it may be of interest to design a clinical trial of an antiviral agent to determine whether antiviral therapeutics may improve management of MIS-C.

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Table 1: Selected laboratory values obtained on admission.

Lab Test	Patient's Results	Reference Levels
Human Herpesvirus 6 DNA Quantification	1,123,094 copies/mL	<500 copies/mL
Epstein-Barr Virus Ab VCA IgM	<36 unit/mL	<36 unit/mL
Epstein-Barr Virus Ab VCA IgG	<18 unit/mL	<18 unit/mL
Cytomegalovirus IgM Ab	<30 AU/mL	<30 AU/mL
Cytomegalovirus IgG Ab	<0.60 unit/mL	<0.60 unit/mL
Human Immunodeficiency Virus 1+2 p24	Nonreactive	Nonreactive
Parvovirus IgM Ab	0.2	<0.9
Parvovirus IgG Ab	0.2	<0.9
Herpes Simplex Virus 1+2 PCR	Negative	Negative
Immunoglobulin G	822 mg/dL	685-1620 mg/dL
Immunoglobulin M	75 mg/dL	27-151 mg/dL
Rheumatoid Factor	<10 Int_unit	<10 Int_unit
Antinuclear Antibody screen by ELISA	Negative	Negative
Antistreptolysin O Titer	100 Int_unit	<100 Int_unit
Thyroid-stimulating Hormone	0.39 mIU/L	0.30-5 mIU/L
Free T4	0.78 ng/dL	0.73-1.80 ng/dL
BUN	36 mg/dL	7-17 mg/dL
Creatinine	2.3 mg/dL	0.5-0.8 mg/dL
Aspartate Aminotransferase	926 U/L	<35 U/L
Alanine Transaminase	384 U/L	<55 U/L
White Blood Cells	14.04 k/uL	4.40-9.50 k/uL
Hemoglobin	12 g/dL	11.5-15.5 g/dL
Hematocrit	34.8%	40-52%
Platelets	107 k/uL	150-450 k/uL
Protime	22.2 sec	9-13 sec
International Normalized Ratio (INR)	2.0	0.8-1.2
Partial Thromboplastin Time	49.6 sec	25.0-36.0 sec

D-Dimer	3,203 ng/mL DDU	<= 230 ng/mL DDU
Fibrinogen	734 mg/dL	151-402 mg/dL
Ferritin	6,907 ng/mL	20-275 ng/mL
C-reactive Protein	41.6 mg/dL	<0.5 mg/dL
Erythrocyte Sedimentation Rate	80 mm/h	0-30 mm/h
Lactate Dehydrogenase	1158 U/L	127-287 U/L
Gamma-Glutamyl Transferase	18 U/L	<55 U/L
Lipase	24 U/L	8-78 U/L
B Type Natriuretic Peptide	618 pg/mL	<13 pg/mL
Troponin I	1.76 ng/mL	<0.02 ng/mL

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