iciHHV-6 in a Patient With Multisystem Inflammatory Syndrome in Children

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Multisystem inflammatory syndrome in children (MIS-C) is a serious, sometimes life-threatening late complication of coronavirus disease 2019 (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. Human herpesvirus 6 (HHV-6), the virus responsible for roseola, is a ubiquitous herpesvirus that causes 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 human herpesvirus 6 (iciHHV-6), which is HHV-6 that has been integrated into chromosomal telomeric regions and is transmitted through the germ line. iciHHV-6 can be reactivated and has been associated with altered immune responses. We report here a case of MIS-C in which an initial high HHV-6 DNA polymerase chain reaction viral load assay prompted testing for iciHHV-6, which yielded a positive result. Additional research may be warranted to determine if 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 coronavirus disease 2019 (COVID-19).[1–6] The MIS-C case definition includes at least 2 of the following 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 (interleukin 6, interleukin 17A, and interleukin 18, interferon-γ, and tumor necrosis factor β), and lymphocytes of patients with MIS-C 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral loads (VLs) have become undetectable.[6] The incidence of MIS-C is difficult to establish because many children experience asymptomatic SARS-CoV-2 infection.[5] Although there

abstract

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are many descriptions of the features of MIS-C, including important immunologic 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 of the SARS-CoV-2 spike protein 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, a syndrome that can be caused by human herpesvirus 7 also[17]), is a ubiquitous human pathogen[18–20] with 2 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 to 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.[23] The cellular receptor for HHV-6A is CD46,[24] which is found on all nucleated cells, whereas 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 human herpesvirus 6 (iciHHV-6), which can be transmitted in a Mendelian fashion.[26–29] The presence of iciHHV-6 has been associated with altered and, in some instances, increased 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 HHV-6 and iciHHV-6 can be reactivated from latency.[28]. HHV-6 reactivation, accompanied by 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,[35,36] which has been linked to elevated proinflammatory cytokine levels.[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 human herpesvirus 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 such as fever, bone marrow suppression, interstitial pneumonitis, and encephalitis.

Here we report a case of a patient with MIS-C who was initially found to have a high HHV-6 VL and then subsequently determined to have iciHHV-6.

In late December 2020, a 12-year-old boy with obesity presented to an outside hospital emergency department after 3 days of headache and vomiting and 1 day of altered mental status. He was febrile, hypotensive, and tachycardic on presentation and was ultimately transferred to their PICU 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. The result of 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 40.8°C despite receiving antibiotic and antipyretic treatment. Laboratory studies revealed elevated levels of inflammatory markers, thrombocytopenia, coagulopathy, acute kidney injury, and transaminitis (Table 1). Elevation of troponin and brain natriuretic peptide levels 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 a repeat echocardiogram, and the patient was placed on continuous

TABLE 1 Selected Laboratory Values Obtained on Admission

Laboratory Test	Patient's Results	Reference Levels
HHV-6 DNA quantification, copies per mL	1 123 094	<500
Epstein-Barr virus antibody VCA IgM, U/mL	<36	<36
Epstein-Barr Virus antibody VCA IgG, U/mL	<18	<18
Cytomegalovirus IgM antibody, AU/mL	<30	<30
Cytomegalovirus IgG antibody, U/mL	<0.60	<0.60
HIV 1 and 2 p24	Nonreactive	Nonreactive
Parvovirus IgM antibody	Negative	Negative
Parvovirus IgG antibody	Negative	Negative
Herpes simplex virus 1 and 2 PCR result	Negative	Negative
IgG, mg/dL	822	685–1620
IgM, mg/dL	75	27–151
Rheumatoid factor, IU	<10	<10
Antinuclear antibody screen results by ELISA	Negative	Negative
Anti-streptolysin O titer, IU	100	<100
Thyroid-stimulating hormone, mIU/L	0.39	0.30–5
Free T4, ng/dL	0.78	0.73–1.80
BUN, mg/dL	36	7–17
Creatinine, mg/dL	2.3	0.5–0.8
Aspartate aminotransferase, U/L	926	<35
Alanine transaminase, U/L	384	<55
White blood cell count, ×1000 per μL	14.04	4.40–9.50
Hemoglobin, g/dL	12	11.5–15.5
Hematocrit, %	34.8	40–52
Platelet count, ×1000 per μL	107	150–450
Prothrombin time, s	22.2	9–13
INR	2.0	0.8–1.2
Partial thromboplastin time, s	49.6	25.0–36.0
D-dimer, ng/mL	3203	≤230
Fibrinogen, mg/dL	734	151–402
Ferritin, ng/mL	6907	20–275
C-reactive protein, mg/dL	41.6	<0.5
Erythrocyte sedimentation rate, mm/h	80	0–30
Lactate dehydrogenase, U/L	1158	127–287
γ-glutamyl transferase, U/L	18	<55
Lipase, U/L	24	8–78
B-type natriuretic peptide, pg/mL	618	<13
Troponin I, ng/mL	1.76	<0.02

ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; PCR, polymerase chain reaction; SUN, serum urea nitrogen; T4, thyroxine; VCA, viral capsid antibody.

vasoactive infusions to maintain adequate perfusion. He had severe cardiac dysfunction and acute respiratory failure requiring intubation. Given multisystem involvement, with increasing suspicion for MIS-C, he was treated with intravenous immunoglobulin. Although the patient had no known history of COVID-19 infection or any other recent illnesses, a COVID-19 immunoglobulin G serological test, by using a pre–intravenous immunoglobulin serum sample, was obtained, and the result was found to be positive, confirming suspicion for MIS-C. He was transferred from the referring hospital to the University of Virginia for further management.

At the University of Virginia, the result of one repeat SARS-CoV-2 RT-PCR assay was positive at a high cycle threshold value of 40 cycles, and the result of another repeat SARS-CoV-2 RT-PCR was negative. After initiation of anakinra, an interleukin 1 inhibitor, and high-dose methylprednisolone, he showed improvement in laboratory markers and clinical status. He was weaned from his vasopressor support and extubated to room air and showed return of his end-organ function. Antibiotics were discontinued after results of bacterial cultures remained negative. Results of viral pathogen testing sent by the referring hospital at the time of his initial admission returned negative for cytomegalovirus, Epstein-Barr virus, HIV, herpes simplex virus, and parvovirus (Table 1). However, an HHV-6 polymerase chain reaction result sent by the referring hospital, conducted by Quest Diagnostics Nichols Institute Chantilly (Chantilly, VA) later revealed a high VL of 1 123 094 viral DNA copies per mL (reference range <500 viral DNA copies per 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 leukocytes. 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 those seen in MIS-C are known to be associated with HHV-6 activation, including in patients with iciHHV-6. In addition, proapoptotic 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 patients with MIS-C, 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, in which high-level HHV-6 activation has not been commonly observed.

Here we report a single case of iciHHV-6 in association with MIS-C. Although no definitive conclusions can be drawn from a single case, it may be useful to study larger numbers of patients with MIS-C to determine if iciHHV-6 is commonly observed in association with MIS-C, particularly considering the observations that patients with MIS-C can demonstrate enhanced antibody responses to SARS-CoV-2[13–15] and that 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 patients with MIS-C 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 US Food and Drug Administration–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 if antiviral therapeutics may improve management of MIS-C.

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ABBREVIATIONS

COVID-19: coronavirus disease 2019
HHV-6: human herpesvirus 6
iciHHV-6: inherited chromosomally integrated human herpesvirus 6
MIS-C: multisystem inflammatory syndrome in children
RT-PCR: reverse transcription polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
VL: viral load

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REFERENCES

1. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771–1778
2. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094
3. Whittaker E, Bamford A, Kenny J, et al; PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020;324(3):259–269
4. Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. *JAMA*. 2020;324(3):294–296
5. Dufort EM, Koumans EH, Chow EJ, et al; New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med*. 2020;383(4):347–358
6. Feldstein LR, Rose EB, Horwitz SM, et al; Overcoming COVID-19 Investigators; CDC

COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383(4):334–346

7. World Health Organization. *Multisystem Inflammatory syndrome in Children and Adolescents With COVID-19*. Geneva, Switzerland: World Health Organization; 2020
8. Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol*. 2020;77(11):1440–1445
9. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. 2020;143(10):3104–3120
10. Gruber CN, Patel RS, Trachtman R, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). *Cell*. 2020;183(4):982–995.e14
11. Consiglio CR, Cotugno N, Sardh F, et al; CACTUS Study Team. The immunology of multisystem inflammatory syndrome in children with COVID-19. *Cell*. 2020;183(4):968–981.e7
12. Brodsky NN, Ramaswamy A, Lucas CL. The mystery of MIS-C post-SARS-CoV-2 infection. *Trends Microbiol*. 2020;28(12):956–958
13. Yonker LM, Neilan AM, Bartsch Y, et al. Pediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): clinical presentation, infectivity, and immune responses. *J Pediatr*. 2020;227:45–52.e5
14. Rostad CA, Chahroudi A, Mantus G, et al. Quantitative SARS-CoV-2 serology in children with multisystem inflammatory syndrome (MIS-C). *Pediatrics*. 2020;146(6):e2020018242
15. Zeichner SL, Cruz AT. Multisystem inflammatory syndrome in children and SARS-CoV-2 serology. *Pediatrics*. 2020;146(6):e2020032888
16. Bartsch YC, Wang C, Zohar T, et al. Humoral signatures of protective and pathological SARS-CoV-2 infection in children. *Nat Med*. 2021;27(3):454–462
17. Hall CB, Caserta MT, Schnabel KC, et al. Characteristics and acquisition of human herpesvirus (HHV) 7 infections in relation to infection with HHV-6. *J Infect Dis*. 2006;193(8):1063–1069
18. Flamand L, Komaroff AL, Arbuckle JH, Medveczky PG, Ablashi DV. Review, part 1: human herpesvirus-6-basic biology, diagnostic testing, and antiviral efficacy. *J Med Virol*. 2010;82(9):1560–1568
19. Yao K, Crawford JR, Komaroff AL, Ablashi DV, Jacobson S. Review part 2: human herpesvirus-6 in central nervous system diseases. *J Med Virol*. 2010;82(10):1669–1678
20. Caserta MT, Mock DJ, Dewhurst S. Human herpesvirus 6. *Clin Infect Dis*. 2001;33(6):829–833
21. Ablashi D, Agut H, Alvarez-Lafuente R, et al. Classification of HHV-6A and HHV-6B as distinct viruses. *Arch Virol*. 2014;159(5):863–870
22. Hall CB, Long CE, Schnabel KC, et al. Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. *N Engl J Med*. 1994;331(7):432–438
23. De Clercq E, Naesens L, De Bolle L, Schols D, Zhang Y, Neyts J. Antiviral agents active against human herpesviruses HHV-6, HHV-7 and HHV-8. *Rev Med Virol*. 2001;11(6):381–395
24. Liszewski MK, Post TW, Atkinson JP. Membrane cofactor protein (MCP or CD46): newest member of the regulators of complement activation gene cluster. *Annu Rev Immunol*. 1991;9:431–455
25. Tang H, Serada S, Kawabata A, et al. CD134 is a cellular receptor specific for human herpesvirus-6B entry. *Proc Natl Acad Sci U S A*. 2013;110(22):9096–9099
26. Flamand L. Chromosomal integration by human herpesviruses 6A and 6B. *Adv Exp Med Biol*. 2018;1045:209–226
27. Pellett PE, Ablashi DV, Ambros PF, et al. Chromosomally integrated human herpesvirus 6: questions and answers. *Rev Med Virol*. 2012;22(3):144–155
28. Pantry SN, Medveczky PG. Latency, integration, and reactivation of human herpesvirus-6. *Viruses*. 2017;9(7):194
29. Kaufer BB, Flamand L. Chromosomally integrated HHV-6: impact on virus, cell and organismal biology. *Curr Opin Virol*. 2014;9:111–118
30. Peddu V, Dubuc I, Gravel A, et al. Inherited chromosomally integrated human herpesvirus 6 demonstrates tissue-specific RNA expression *in vivo* that correlates with an increased antibody immune response. *J Virol*. 2019;94(1):e01418–e01419
31. Hill JA, Magaret AS, Hall-Sedlak R, et al. Outcomes of hematopoietic cell transplantation using donors or recipients with inherited chromosomally integrated HHV-6. *Blood*. 2017;130(8):1062–1069
32. Zerr DM, Corey L, Kim HW, Huang ML, Nguy L, Boeckh M. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. *Clin Infect Dis*. 2005;40(7):932–940
33. Hill JA, Nichols WG, Marty FM, et al. Oral brincidofovir decreases the incidence of HHV-6B viremia after allogeneic HCT. *Blood*. 2020;135(17):1447–1451
34. Ogata M, Satou T, Kadota J, et al. Human herpesvirus 6 (HHV-6) reactivation and HHV-6 encephalitis after allogeneic hematopoietic cell transplantation: a multicenter, prospective study. *Clin Infect Dis*. 2013;57(5):671–681
35. Ichiche M, Kiesch N, De Bels D. DRESS syndrome associated with HHV-6 reactivation. *Eur J Intern Med*. 2003;14(8):498–500
36. Ahluwalia J, Abuabara K, Perman MJ, Yan AC. Human herpesvirus 6 involvement in paediatric drug hypersensitivity syndrome. *Br J Dermatol*. 2015;172(4):1090–1095
37. Yoshikawa T, Fujita A, Yagami A, et al. Human herpesvirus 6 reactivation and inflammatory cytokine production in patients with drug-induced hypersensitivity syndrome. *J Clin Virol*. 2006;37(suppl 1):S92–S96
38. Kondo K, Yamanishi K. HHV-6A, 6B, and 7: molecular basis of latency and reactivation. In: Arvin A, Campadelli-Fiume G, Mocarski E, et al, eds. *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Cambridge, United Kingdom: Cambridge University Press; 2007
39. Prasad A, Lu M, Lukac DM, Zeichner SL. An alternative Kaposi's sarcoma-associated herpesvirus replication program triggered by host cell apoptosis. *J Virol*. 2012;86(8):4404–4419
40. Khan SZ, Hand N, Zeichner SL. Apoptosis-induced activation of HIV-1 in latently infected cell lines. *Retrovirology*. 2015;12:42
41. Ogata M, Phan TL, Fukuda T. Antiviral therapy for the treatment of HHV-6-associated syndromes after transplant. *Am J Transplant*. 2019;19(1):306–307
42. Zerr DM, Gupta D, Huang ML, Carter R, Corey L. Effect of antivirals on human herpesvirus 6 replication in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2002;34(3):309–317

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