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CASE REPORT

Multisystem Inflammatory Syndrome in Children in February 2020 and Implications of Genomic Sequencing for SARS-CoV-2

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Multisystem inflammatory syndrome in children (MIS-C) is a newly recognized disease process that can complicate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We present what we believe to be the earliest case of MIS-C, occurring in February 2020. Our patient's SARS-CoV-2 infection was caused by an emerging lineage with the D614G variant in the spike protein. This lineage would subsequently become the predominant cause of SARS-CoV-2 outbreaks in Europe and the United States where MIS-C was first described.

Key words. COVID-19; D614G; MIS-C; pseudotumor cerebri syndrome; SARS-CoV-2; viral lineage.

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began circulating in late 2019 within China, multisystem inflammatory syndrome in children (MIS-C) was not reported until April 2020. This complication has still not been reported in Asia, including retrospectively, despite numerous accounts of children with SARS-CoV-2 infections. However, it was described almost simultaneously in multiple patients by physicians in Europe and the United States [1, 2]. Coincidentally, we now recognize that there was a global shift in the lineage of SARS-CoV-2 causing clinical disease that occurred in March 2020 [3]. Some speculate that the development of MIS-C could be due to the changes in pathogenicity associated with certain viral lineages of SARS-CoV-2 [4]. Our patient presented before this shift had been observed when the majority of SARS-CoV-2 lineages observed in the United States matched those reported within China [3, 5].

CASE

On February 22, 2020, a 9-year-old boy presented to an emergency department in Pierce County Washington with a 7-day history of subjective fevers, body aches, and cough followed by the development of abdominal pain and diarrhea. Multiple family members were also recovering from similar flu-like symptoms. He had no recent travel or known exposures to SARS-CoV-2. On examination, he was febrile to 40.4°C. Initial labs were notable for lymphopenia with an absolute lymphocyte count of 500 cells/μL, mild hyponatremia, and elevated inflammatory markers with a C-reactive protein of 30.4 mg/dL and an erythrocyte sedimentation rate of 118 mm/hour. A nasopharyngeal swab was tested against a multi-pathogen molecular assay that detected rhino/enterovirus and was otherwise negative. Testing for SARS-CoV-2 was not undertaken at this time. He was admitted for observation. On hospital day 2, he defervesced though continued to be tachycardic with heart rate averaging 120 beats per minute. His electrocardiogram was consistent with sinus tachycardia; chest x-ray demonstrated multifocal peribronchial thickening. The following day he developed increased work of breathing requiring respiratory support. A repeat chest x-ray now showed diffuse interstitial opacities along with cardiomegaly. His procalcitonin was elevated at 12.95 ng/mL. Concurrent to this, he was noted to have tea-colored urine with urinalysis revealing blood, pyuria, and proteinuria. His urine protein to creatinine ratio was 0.93 and C3/C4 levels, antistreptolysin O, and anti-DNAse B titers were within normal limits. An N-terminal Pro B-type natriuretic peptide and high sensitivity troponin-T were elevated at 35 270 pg/mL and 88 ng/L, respectively. He was transferred to the pediatric intensive care unit where a transthoracic echocardiogram revealed a small pericardial effusion, normal coronary arteries, and preserved left ventricular systolic function. On hospital day 4, he developed a truncal macular rash with targetoid lesions, edematous hands, edematous and erythematous eyelids, nonexudative conjunctivitis, and oral mucositis. At this time, his fevers also recurred. He was empirically treated with courses of ceftriaxone, doxycycline, and intravenous immunoglobulin.

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Initial SARS-CoV-2 testing of a nasopharyngeal swab was performed on the day of illness 16 (hospital day 9) using the Centers for Disease Control (CDC) 2019-Novel Coronavirus (2019-nCoV) real-time reverse-transcriptase polymerase chain reaction (RT-PCR) Diagnostic Panel. This revealed a low positivity with primer_N1 (positivity at cycle threshold 36.2 with negative detection at cycle threshold 40.0) but was negative for primer_N2. Repeat testing of the same sample and new samples that were obtained the following day were all negative against both primers. This case was discussed with experts at the CDC who did not approve further investigation as a possible case of SARS-CoV-2. An extensive workup for additional infectious and autoimmune etiologies was otherwise unrevealing. The patient clinically improved without evidence of chronic end-organ dysfunction, and he was discharged on hospital day 11. He re-presented 3 days later, after a routine optometry visit uncovered bilateral optic nerve edema. A subsequent MRI of his brain and orbits demonstrated flattening of the globes at the optic discs. His lumbar puncture had an increased opening pressure of 31 cm H_20 although fluid analysis was normal. The patient was subsequently treated with acetazolamide.

His case was revisited due to the similarities that it shared with reports of MIS-C. Antibody testing performed 83 days after illness, using The Elecsys Anti-SARS-CoV-2 Total Antibody from Roche, showed no detectable SARS-CoV-2 immunoglobulin G. Genomic sequencing of his stored nasopharyngeal swab that was obtained at the time of hospital admission (February 22, 2020), using ARTIC V3 primers, (https://artic.network/ncov-2019), recovered 93% of the SARS-CoV-2 genome at 15× depth when compared with the Wuhan-Hu-1 (NC 045512.2) RefSeq genome. The assembled genome was consistent with Global Initiative on Sharing Avian Influenza Data (GISAID) clade GR (D614G and N-G204R) and has been deposited on GISAID (EPI ISL 644823).

DISCUSSION

MIS-C is defined by the CDC as a person younger than 21 years old with fever, signs of inflammation, multisystem organ involvement, and with current or recent SARS-CoV-2 infection based on laboratory evidence or an epidemiologic link to infection. Similar to our patient, there are a minority of those who fit the clinical description of MIS-C with negative PCR and serologic testing and no known exposure to an infected source. Genomic sequencing is not a common mode of SARS-CoV-2 diagnosis. However, the initial workup of this patient was limited by the lack of antibody testing availability and the CDC's SARS-CoV-2 testing indications. The original nasopharyngeal swab, obtained at hospital admission and subsequently used for genomic testing, could not be used for SARS-CoV-2 PCR testing because it did not meet the storage criteria outlined within the 2019-nCoV Emergency Use Authorization. However, PCR sensitivity declines outside the acute phase of infection; therefore, it is not surprising that this patient had an indeterminate or negative test after 2 weeks of symptoms. The lack of detectable antibody responses in this patient also does not preclude the possibility of MIS-C; SARS-CoV-2 antibodies may drop to a level below the limit of detection in less than 60 days [6].

Previous investigation has suggested that the outbreak in Washington State began with an introduction of the virus in late January or early February 2020, with a strain similar to those identified from outbreaks in China [5]. The G clade, representing the D614G variant, was not identified in the United States until late February, but it quickly became the dominant lineage circulating within the United States by mid-March [3]. This patient's symptoms began on February 15, and, therefore, he was probably among the earliest to be infected by this lineage in the United States [3]. He was infected with a strain that was likely introduced separately from the initial Washington cases [5]. His was a community-acquired case, with no known epidemiologic links; this case provides evidence that early community transmission was from multiple sources and also highlights some of the deficiencies in our initial surveillance.

MIS-C cases were described when the circulation of D614G was increasing worldwide [3]. Not only is this patient among the first to reportedly have MIS-C, but he was also infected by what was presumably a newly evolved lineage of SARS-CoV-2. Development of MIS-C in this patient and not others, at a time when isolation of D614G was rare, suggests that the risk of developing MIS-C as a complication of SARS-CoV-2 infection may be associated with viral lineage. Further genomic characterization of pediatric patients with and without MIS-C could help clarify this matter. Of note, this case also adds to the limited description of pseudotumor cerebri syndrome as a possible complication of MIS-C [7, 8].

Notes

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Patient and other consents. Parental consent was given for the publication of this case. "The views expressed are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense, or the U.S. Government."

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