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Anne H. Rowley, M.D.

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Multisystem Inflammatory Syndrome in Children (MIS-C) and Kawasaki Disease: Two Different Illnesses with Overlapping Clinical Features

Anne H. Rowley, M.D.

Professor of Pediatrics and of Microbiology and Immunology

Northwestern University Feinberg School of Medicine

The Ann & Robert H. Lurie Children's Hospital of Chicago

Chicago, IL

Correspondence:

Anne H. Rowley, M.D.

The Ann & Robert H. Lurie Children's Hospital of Chicago

225 E Chicago Avenue, Box #205

Chicago, IL 60611

a-rowley@northwestern.edu

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In late April 2020, alarming news emerged from Europe that a group of children with evidence of recent SARS-CoV-2 infection had developed a severe illness, manifesting fever, hypotension requiring inotropic support, severe abdominal pain, and myocardial dysfunction with marked elevation in cardiac damage markers. This syndrome has been named Pediatric Multisystem Inflammatory Syndrome in Europe, and Multisystem Inflammatory Syndrome in Children (MIS-C) by the U.S. Centers for Disease Control (CDC). As case series began to be reported, the similarities in the clinical features among the cases were striking, as were the frequent additional laboratory features of lymphopenia, thrombocytopenia, and cytokine storm with marked elevation in serum inflammatory markers including interleukin-6 (IL-6)(1-6,6A,6B). Most of these children recovered, although infrequently patients have required extracorporeal membrane oxygenation, with a fatal outcome from complications of this therapy reported rarely (3,6A). Patients were managed in different ways, often with corticosteroid therapy, intravenous gammaglobulin, and, less often, anti-cytokine therapies, and the vast majority appeared to require intensive care therapy only for a matter of days, regardless of the management strategy (1, 5, 6, 6A,6B). Some patients had one or more clinical features that can be observed in many illnesses of childhood including Kawasaki disease, such as conjunctival injection, oral erythema, and rash. Classic KD diagnostic criteria were rarely present. Moreover, the median age of the cases was 9-10 years in the largest series reported to date (1, 7), which is in marked contrast to KD, which occurs predominately in children $\leq$5 years of age and with a peak incidence at ~10 months of age (8, 9). Asian children have the highest attack rates of KD, whereas the highest rates of MIS-C have been in children of African descent (3, 10). These marked epidemiologic differences make it clear that the two conditions are not the same.

Because of a concern that MIS-C might potentially encompass a wider range of clinical features than those observed in the reported cases, the CDC developed a broad case definition. Unfortunately, the case definition as it currently stands is problematic, because patients with

many infectious and inflammatory conditions of childhood that are not MIS-C fulfill the case definition. This includes patients with acute COVID-19 infection (eg, acute infection with fever, rash, diarrhea, and a minimally elevated C-reactive protein level), classic KD (e.g., a child with KD who has rash as one of the diagnostic features and mild hepatitis or diarrhea), other viral infections (e.g. one of many that could cause fever, rash, cough, and an increase in neutrophils in peripheral blood), systemic onset juvenile idiopathic arthritis (e.g., fever, rash, an increase in neutrophils in peripheral blood, elevated acute phase reactants), and so on. Moreover, on my recent clinical service, I noted an increase in patient transfers from referring hospitals of children with low grade fever for one day, rash, and mild abdominal discomfort, for evaluation for possible MIS-C. These children arrived appearing well, with completely normal blood pressure and heart rate and minimally elevated acute phase reactants. Presumably, all the media publicity about MIS-C is raising concern among practitioners about missing this diagnosis, potentially resulting in an increase in hospital admissions for routine minor childhood illnesses, and a likely inflated number of reported cases. Moreover, a rapid or presumptive diagnosis of MIS-C, which remains uncommon, also has the potential to result in premature diagnostic closure in children who fulfill the broad case definition but in reality have a potentially life-threatening, non-MIS-C illness.

It is problematic that some similar clinical features of MIS-C and incomplete KD can lead to diagnostic uncertainty in individual patients. This scenario reminds me of my clinical experience in the late 1980s and early 1990s in Chicago when we were experiencing a different viral epidemic, due to measles. During that time, it was startling to see how closely the clinical features of KD resembled those of measles. Our approach at that time to differentiate the conditions was to perform a measles IgM antibody test, run daily in our hospital during the epidemic, and if the test was negative, treat the patient for KD. Measles is one of the few infectious diseases that virtually always is symptomatic, so a positive test result confirmed the

diagnosis. The present COVID-19 epidemic does not offer such a straightforward solution to the diagnostic dilemma. Not only is there no diagnostic test for KD at present, but asymptomatic or mildly symptomatic SARS-CoV-2 infection is prevalent enough in children in many areas of the U.S. and abroad at the present time that even a positive RT-PCR or serologic test for SARS-CoV-2 antibody does not necessarily mean that a child's presenting illness is related to SARS-CoV-2. With routine RT-PCR screening of hospitalized patients, we find occasional positive results in children admitted with fractures, for routine surgical procedures, and with a variety of other clinical problems not related to SARS-CoV-2 infection. In addition, antibody positivity is very likely to be increasing over time in the population. Understandably, diagnostic confusion can result, and incorrect diagnoses may be assigned. To add to this confusion, some patients with MIS-C are reported to have developed mild coronary artery dilation (1, 2, 10) or rarely, aneurysms (3, 4, 7). That mild transient coronary artery dilation can develop as a result of cytokine storm with high IL-6 levels has been demonstrated in systemic onset juvenile idiopathic arthritis (11), and mild transient coronary dilation could be the result of a similar cytokine storm in MIS-C. Persistent coronary artery aneurysms and their complications, however, have previously only been attributed to KD in pediatric patients. Because of the clinical similarities in the two conditions, it is possible that patients reported as having MIS-C with persisting aneurysms actually had KD. Fortunately, patients with KD and MIS-C both improve with intravenous gammaglobulin and corticosteroid therapy, although the efficacy of any therapy for MIS-C is evolving and is as yet is unproven. If SARS-CoV-2 can result in persisting coronary artery aneurysms, it would be noteworthy, as it would be the first virus proved to do so.

For patients in whom MIS-C and KD are being considered, some clinical and laboratory features of the two conditions may help in discerning the correct diagnosis. Abdominal pain significant enough to prompt advanced imaging and surgical consultation occurs rarely in KD (10a) but is characteristic of MIS-C. Lymphopenia is a typical finding in MIS-C and is reported

rarely in KD; the more severe the lymphopenia, the more likely the diagnosis is MIS-C. Although NT-pro-BNP is a biomarker of potential value in KD and some patients have been reported to have levels as high as 7,000 pg/mL (12, 13), the extent of the elevation in KD generally is lower than in MIS-C, for which values in excess of 10,000 pg/mL often are reported; the higher the NT-pro-BNP level, the more likely the diagnosis is MIS-C. Myocardial dysfunction as assessed by echocardiography is common in MIS-C and is rare in KD..

Some investigators have proposed that MIS-C, while having very different epidemiologic and some different laboratory features compared with KD, could provide etiologic clues that KD may result from infection with a coronavirus (4, 10). The Table outlines some differing features of KD and coronavirus infections that make an etiologic relationship unlikely. Moreover, if SARS-CoV-2 or a closely related virus was a KD etiologic agent, one would expect the epidemiology of MIS-C and KD to be similar. Of note, MIS-C cases have not been observed in China (14) or Japan, countries with the highest prevalence of KD in the world, which surely should have been expected if there was an etiologic relationship between KD and MIS-C.

Many favor the theory that diverse infectious agents (including coronavirus) can trigger a “final common pathway” of immune dysregulation causing KD in a genetically susceptible individual. However, the idea that a genetically predisposed individual who is immunologically susceptible to multiple infections could be triggered only once (since KD rarely recurs) does not fit with our present understanding of human immunology. This hypothesis would also predict that KD could occur at any age, whereas the age distribution of KD is quite classic for a disease caused by a single ubiquitous infectious agent. One also cannot explain the occurrence of well-documented epidemics and outbreaks of KD with geographic wave-like spread of illness (15) based on a theory of diverse infectious triggers.

MIS-C cases have appeared during periods of high prevalence of COVID-19 in an individual country, and also appear to decrease following a decline in COVID-19 cases (16). It is

hoped that when the SARS-CoV-2 pandemic is finally overcome, potentially by vaccination, MIS-C will no longer be a clinical issue. Although the etiologic agent of KD presently remains unclear, research studies support a ubiquitous RNA virus, different from presently known human viruses, that forms intracytoplasmic inclusion bodies in tissues from patients with KD (17, 18). We have identified a protein epitope of the putative agent recognized by the antibody response in KD patients, with substantial progress in developing the first-ever serologic assay for KD (18). Development of a diagnostic test for KD would enable distinguishing KD from the many infectious and inflammatory conditions in the differential diagnosis (19), which presently should include MIS-C. In the meantime, research is urgently needed to identify the pathogenesis of MIS-C, which is currently unknown but bears similarities to the cytokine storm observed in adult patients with COVID-19 during their second week of illness(20).

Table. Distinct Features of Kawasaki Disease and Coronavirus Infections

Kawasaki Disease	Coronavirus Infections
No virus can be isolated from cultures of clinical specimens (21, 22)	Virus can be isolated from cultures of clinical specimens
No coronavirus is identified by high throughput RNA sequencing of tissues from KD patients (18, 23, 24)	Virus can be identified by high throughput RNA sequencing of tissues from infected patients
No signal exists for serologic cross reactivity with coronaviruses, even using new highly sensitive VirScan method (21-23)	Serologic cross reactivity occurs with other coronaviruses, particularly those in the same subfamily (25)
Recurrence is rare; disease is rare in adolescents and adults	Immunity wanes and infections with most coronaviruses generally recur lifelong (26)
Numerous RT-PCR studies investigating coronavirus as potential cause have been negative	Viral RNA is consistently detected in patient samples by RT-PCR
Inclusion bodies have been identified in ciliated bronchial epithelium that are targeted by antibodies from KD patients (18); virus-like particles found adjacent to inclusion bodies are about 50 nm in diameter (17)	No inclusion bodies are identifiable in bronchial epithelium; virus particles are ~120 nm in diameter
Patients have an antigen-driven immune response that is not directed at coronavirus (18)	Immune response is directed at coronavirus
Coronary artery aneurysms occur; thrombosis is limited to within aneurysms	Hypercoagulability with vascular thrombosis at multiple sites is characteristic of SARS-CoV-2 infection; coronary artery aneurysms are not reported in acute SARS-CoV-2 infection; autopsy in the only pediatric patient reported to date with cardiac death from SARS-CoV-2 showed eosinophilic myocarditis with no evidence of vascular inflammation(27)
Epidemiologic and histologic evidence supports the hypothesis of persistent infection (28, 29)	There is no persistent infection
Median age of patients with KD-associated shock is 2.8 yrs (30)	Median age of patients with SARS-CoV-2 associated pediatric shock is is 9-10 years (1, 7)

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