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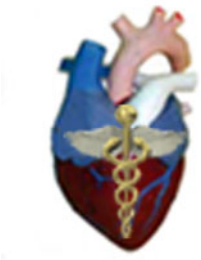

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EDITORIAL

Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-Cov-2 Infection (PIMS-TS): Kawasaki-Like Multisystem Inflammatory Syndrome in Children (MIS-C) During the COVID-19 Pandemic with Predominant Myocarditis

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Abstract

During the COVID-19 pandemic, a Kawasaki-like multisystem inflammatory syndrome with predominant myocarditis associated with SARS-CoV-2 infection has recently been reported, now referred to as Multisystem Inflammatory Syndrome in Children (**MIS-C**) Associated with COVID-19, or Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 infection (**PIMS-TS**). These pediatric patients present with features that overlap features of Kawasaki Disease (KD) and toxic shock syndrome, albeit with distinct differences that relate to more common myocardial involvement requiring vasopressor support in PIMS-TS/MIS-C compared to KD (~50% vs ~5%), and less common coronary artery aneurysms (~9% vs ~25%). PIMS-TS/MIS-C seems to be largely immune-mediated, triggered by COVID-19, with the induced hyperinflammatory syndrome possibly due to post-infectious cytokine storm, rather than a result of direct cell injury caused by the virus. Treatment of this syndrome is similar to KD and includes intravenous immunoglobulin (IVIG), corticosteroids, and antiplatelet agents, while a few patients have also received interleukin-6 (IL-6) inhibitors. ***Rhythmos*** 2020;15(3):42-46.

Key Words: Kawasaki disease; COVID-19; vasculitis; coronavirus; cardiovascular; myocarditis; cytokine storm

Abbreviations: CV = cardiovascular; ICU = intensive care unit; IL = interleukin; KD = Kawasaki disease; **MIS-C** = Multisystem Inflammatory Syndrome in Children; **PIMS-TS** = Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 infection; STING = stimulator of interferon genes

Introduction

Kawasaki disease (KD), also occasionally called mucocutaneous lymph node syndrome, is an acute vasculitis occurring predominantly in children <5 years of age as a self-limited febrile illness of unknown cause that leads to *coronary artery aneurysms* in ~25% of untreated cases.[1] The diagnosis of classic KD is based on the presence of ≥5 days of fever and the presence of ≥4 of the 5 principal clinical features that include erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival

injection with no exudate; maculopapular, diffuse erythroderma, or multiforme-like erythema; erythema and edema of the hands and feet in the acute phase and/or periungual desquamation in the subacute phase; cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral.

Cardiovascular (CV) manifestations of the disease include myocarditis, pericarditis, valvular regurgitation, shock; coronary and/or medium-sized non-coronary artery aneurysms; peripheral gangrene; aortic root dilation.[1]

During the recent COVID-19 pandemic, a Kawasaki-like multisystem inflammatory syndrome with predominant myocarditis associated with COVID-19 infection was reported to the Centers of Disease Control and Prevention (CDC) of the US. A CDC Health advisory was issued on May 14, 2020 providing a case definition of this Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19 (https://emergency.cdc.gov/han/2020/han00432.asp) (**Table 1**)

These pediatric patients present with features that overlap features of Kawasaki disease and toxic shock syndrome. Some individuals may fulfill full or partial criteria for Kawasaki disease. CDC urged that MIS-C should be considered in any pediatric death with evidence of SARS-CoV-2 infection.

This Kawasaki-like disease has been termed multisystem inflammatory syndrome in children (**MIS-C**) by the CDC (**Table 1**), while the WHO has called it pediatric multisystem inflammatory syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (**PIMS-TS**) (**Table 2**).[2]

Recently 21 children and adolescents (median age 7.9 years;57% of African ancestry) admitted with features of Kawasaki disease over a 15-day period were described, of whom 12 (57%) presented with Kawasaki disease shock syndrome and 16 (76%) with myocarditis; 17 (81%) required intensive care support; 19 (90%) had evidence of recent SARS-CoV-2 infection.[3] Patients had gastro-intestinal symptoms during the early stage of illness and high levels of inflammatory markers. They all received intravenous immunoglobulin and 10 (48%) also received corticosteroids. All patients had a favorable clinical course (median hospital stay 8 days). Moderate coronary artery dilations were detected in 5 (24%) patients during hospital stay.

Another study reported on 186 patients <21 years of age who presented with MIS-C associated with SARS-CoV-2 infection from across the United States.[4] The majority of patients (70%) had laboratory-confirmed antecedent or concurrent SARS-CoV-2 infection, with no documented underlying conditions. Cardiovascular involvement was common, with almost half receiving vasopressor or vasoactive support and 1 in 12 having coronary-artery aneurysms. Most patients managed in an intensive care unit (ICU); 20% received mechanical ventilator support; 4 patients (2%) died.

Table 1. CDC Health advisory providing a case definition of the **M**ultisystem **I**nflammatory **S**yndrome in **C**hildren (MIS-C) Associated with COVID-19 (https://emergency.cdc.gov/han/2020/han00432.asp)

- An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Table 2. WHO criteria for **P**ediatric **I**nflammatory **M**ultisystem **S**yndrome in children and adolescents **T**emporally related to **S**ARS-COV-2 (PIMS-TS) (www.who.int/news-room/commentaries/ detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19)

- Children and adolescents 0–19 years of age with fever ≥ 3 days
- **AND** two of the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
2. Hypotension or shock
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP)
4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers)
5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)

- **AND**

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin

- **AND**

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes

- **AND**

Evidence of COVID-19 **(**RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19

A time-series analysis suggests that viral respiratory infections, including SAR-CoV-2, could be triggers for Kawasaki disease and indicates the potential timing of an increase in incidence of the disease in COVID-19 epidemics.[5] The authors of this analysis indicate that a similar peak of hospital admissions due to Kawasaki disease was observed in December, 2009, concurrent with the influenza A H1N1 pandemic.

Genetic susceptibility

Stimulator of interferon genes (STING), also known as transmembrane protein 173 (TMEM173) is a protein that in humans is encoded by the TMEM173 gene. STING is the central signaling hub in sensing of viral DNA and plays a role in innate immunity; its activity is essential for antiviral defense.[6] It induces production of type I interferon (IFN) when cells are infected with intracellular pathogens, including viruses. It has been suggested that delayed over-activation of the STING pathway contributes to the pathogenesis of COVID-19 and polymorphisms of the STING pathway could possibly explain the observation of severe and even fatal cases of COVID-infection occurring in certain previously healthy children and young adults, or conversely, mild cases may be encountered in older individuals. The hypothesis is that at risk are variants of TMEM 173, which encodes STING, that are associated with both over-secretion of IFN-β and severity of COVID-19 pneumonitis, and contribute to its pathogenesis.[7]

Importantly, a role of STING has been suggested in some features of vasculitis, like those associated with Kawasaki disease, and STING might also contribute to the delayed onset of arterial aneurysms observed in severe Kawasaki disease. Furthermore, thrombotic coagulopathy has been noted to contribute to the severity of COVID-19 infection, where an excess of venous, arterial, or microvascular associated events have been observed. On the other hand, Kawasaki disease also increases the risk of thrombosis. It has been suggested that overactivation of the STING pathway promotes hypercoagulability through over-expression and release of IFN-β and tissue factor. Thus, investigators urge that better examining of the contribution of the STING pathway to the thrombotic coagulopathy associated with COVID-19 could help better treat the vasculitis induced by COVID and other viruses.[8]

Kawasaki Disease and PIMS-TS/MIS-C

Although both Kawasaki disease and PIMS-TS/MIS-C have certain similarities, they also have distinct differences. Cardiovascular involvement requiring vasopressor support is reported more commonly in PIMS-TS/MIS-C compared to Kawasaki disease (~50% vs ~5%).[1, 4] Myocardial injury is a prominent extrapulmonary manifestation of Covid-19 that has been associated with increased mortality in adults.[9] Coronary-artery aneurysms are a common feature of Kawasaki disease, affecting ~25% of patients within 21 days after disease onset,[10] while this feature has been reported in only ~9% in patients with PIMS-TS/MIS-C.[4]

A recent report of 95 confirmed and 4 suspected MIS-C cases from New York indicated that the emergence of MIS-C coincided with widespread SARS-CoV-2 transmission; furthermore, this hyperinflammatory syndrome with dermatologic, mucocutaneous, and gastrointestinal manifestations was associated with cardiac dysfunction. [11] Specifically, 62% received vasopressor support, 53% had evidence of myocarditis, 80% were admitted to an ICU, and 2 patients succumbed. The median length of hospital stay was 6 days. Among these patients, 31% were aged 0-5 years, 42% 6-12 years, and 26% were 13-20 years of age.

Additional differences between Kawasaki disease and PIMS-TS/MIS-C may relate to the fact that a minority of patients in the latter group have all the typical symptoms of Kawasaki disease. Another important difference is that the profile of cytokines leading to the inflammatory process appears to be distinct in PIMS-TS/MIS-C and Kawasaki disease. In patients with Kawasaki disease, interleukin-1 (IL-1) appears to be the main inflammatory mediator particularly of coronary artery inflammation, while PIMS-TS/MIS-C appears to be driven mainly by IL-6 and IL-8.[12]

Etiology

The specific etiology of Kawasaki disease has remained largely unknown. However, a lot of data indicate a possible viral etiology.[13, 14] The hypothesis is that some children may be genetically predisposed to a stronger inflammatory response to specific viruses. In these children, upon exposure to the specific virus, an exaggerated inflammatory response is triggered which clinically manifests as Kawasaki disease. The association of viral illness to Kawasaki disease has been demonstrated by several studies and many case reports.[14, 15] Even, viral RNA was isolated from cytoplasmic inclusion bodies in children with Kawasaki disease. Among the viruses associated with Kawasaki disease, influenza, adenovirus, enterovirus, Parvovirus, rhinovirus, respiratory syncytial virus, varicella, Epstein-Barr, measles and even coronavirus have been reported.[14-17] Now the association of Kawasaki disease with COVID-19 is also being observed and reported apropos with this pandemic.[4] However, there appear to be some distinct differences in the phenotype of the disease.

Although this entity is triggered by COVID-19, the hyperinflammatory syndrome seen in these children is possibly due to post-infectious cytokine storm, rather than a result of direct cell injury caused by the virus. In this context, more data were recently derived from 8 children hospitalized for symptoms consistent with PIMS-TS but who were PCR-negative for SARS-CoV-2 and were tested for antibodies to viral spike glycoprotein using an ELISA test.[18] Six of the 8 patients required admission to ICU. All patients exhibited significant IgG and IgA responses to viral spike glycoprotein; the IgG isotypes were of the IgG1 and IgG3 subclasses, a distribution similar to that observed in samples from hospitalized adult COVID-19 patients. In contrast, IgG2 and IgG4 were not detected in children or adults; furthermore, IgM was not detected in children, which contrasts with hospitalized adult COVID-19 patients of whom all had positive IgM responses. Thus, the authors of this study concluded that strong IgG antibody responses can be detected in PCR-negative children with PIMS-TS. The low detection rate of IgM in these patients is consistent with infection having occurred weeks previously and that the syndrome onset occurs well after the control of SARS-CoV-2 viral load, implying that the disease is largely immune-mediated.

Thus, the etiology of PIMS-TS/MIS-C that is offered entails extensive production of antigen-antibody immune complexes during COVID-19 infection that cannot be swiftly cleared in some patients who may have dysfunctional complement systems and thus trigger a type III hypersensitivity immune reaction.[19] This cascade of inflammatory type III hypersensitivity leads to protease releases that can disrupt epithelium, mesothelium, and endothelium basement membranes, and trigger a severe systemic inflammatory response. This could continue beyond the subsiding of COVID-19 infection if the first bout of protease attacks on basement membranes has produced new secondary autoantibodies and new uncleared antigen-antibody immune complexes.

Treatment

Initial treatment for Kawasaki disease comprises a single high dose of intravenous immunoglobulin (IVIG) together with aspirin.[1] Adjunctive therapies may include corticosteroids in high-risk patients. For IVIG-resistant patients, alternative therapies may include infliximab and/or cyclosporine; for highly refractory cases, immunomodulatory monoclonal antibody therapy (except TNF-α blockers), cytotoxic agents, or (rarely) plasma exchange may be considered.

Patients with CV involvement may be managed with use of volume expanders, vasoactive agents, and/or transfer to ICU if hypotension and shock develop.[1] Antiplatelet agents are the standard of care for patients with coronary artery aneurysms, while in specific cases with large or expanding coronary aneurysms anticoagulation therapy will be needed, or even thrombolysis or mechanical restoration of coronary flow in cases on coronary thrombosis.

In several reports of patients with PIMS-TS/MIS-C, treatment similar to that employed in Kawasaki disease patients seems to elicit a favorable response and improve patients' clinical status. Most patients receive IVIG and many of them also receive corticosteroids, while a few have also received IL-6 inhibitors.[3, 4] Drugs down-regulating the STING pathway either upstream, like aspirin, IVIG or vitamin D, or downstream, like IL-6 inhibitors or inhibitors of the JAK-STAT pathway, have been suggested for some of these patients, together with antiplatelet therapy to counter the COVID-19-associated thrombotic coagulopathy.[8]

Finally, reports of inflammatory syndromes that mimic Kawasaki disease and/or KD shock syndrome that concern adult patients have recently begun emerging indicating an evolving situation that may warrant prompt recognition and need for treatment with IVIG and steroids in such cases, as well.[20]

Conclusion

Apropos with the COVID-19 pandemic, a Kawasaki-like multisystem inflammatory syndrome with predominant myocarditis associated with COVID-19 infection has recently been reported and named Multisystem Inflammatory Syndrome in Children (**MIS-C**) Associated with COVID-19, or Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 infection (**PIMS-TS**). These pediatric patients present with features that overlap features of Kawasaki disease and toxic shock syndrome. Although both Kawasaki disease and ***PIMS-TS/MIS-C*** have certain similarities, they also have distinct differences. Myocardial involvement requiring vasopressor support is more common in PIMS-TS/MIS-C compared to Kawasaki disease (~50% vs ~5%). Coronary-artery aneurysms are a more common feature of Kawasaki disease rather than in patients with PIMS-TS/MIS-C (~25% vs ~9%).

The specific etiology of KD has remained largely unknown, however, a preponderance of data indicates a possible viral etiology with the hypothesis that some children may be genetically predisposed to a stronger inflammatory response to specific viruses. Similarly, PIMS-TS/MIS-C seems to be largely immune-mediated, triggered by COVID-19, with the hyperinflammatory syndrome seen in these children possibly due to post-

infectious cytokine storm, rather than a result of direct cell injury caused by the virus.

Treatment of patients with PIMS-TS/MIS-C similar to that employed in Kawasaki disease patients seems to elicit a favorable response and improve patients' clinical status. Most patients receive IVIG and many of them also receive corticosteroids, while a few have also received IL-6 inhibitors. Antiplatelet therapy appears important to counter the COVID-19-associated thrombotic coagulopathy.

Finally, cases of PIMS-TS/MIS-C that concern adult patients have recently been reported indicating an evolving situation that may warrant prompt recognition and need for treatment with IVIG and steroids in such cases, as well.

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