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Commentary In-Press Preview

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Is multisystem inflammatory syndrome in children on the Kawasaki syndrome spectrum?

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Abstract

An alarming increase in children presenting with fever, hyperinflammation and multiorgan dysfunction frequently requiring intensive care has been observed after SARS-CoV-2 infection. The illness resembles Kawasaki Disease (KD) with coronary dilatation and aneurysm occurring in some. However, the cardiovascular manifestations were typically on the severe end of the KD spectrum with cardiogenic shock a common presentation together with other features. This led to defining a unique syndrome named multisystem inflammatory syndrome in children (MIS-C). In this issue of the *JCI*, Lee and Day-Lewis et al. and Diori et al. explored the clinical profiles associated with COVID-19 in children. We posit that while splitting MIS-C into a separate disease may aid clinical management decisions, lumping it into the KD pot may better serve to understand pathobiology.

A severe febrile inflammatory illness in children

Early in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic reports from Asia described a mild corona virus disease 2019 (COVID-19) disease course in children (1). However, in late April and early May 2020 investigators from the United Kingdom, Italy and others began reporting clusters of children presenting with a severe febrile inflammatory illness following infection with SARS-CoV-2 (2, 3). The children presented with multi-system inflammation, which, like Kawasaki disease (KD) had a predilection for the cardiovascular system but was occurring more often than the expected KD incidence. Myocarditis, myocardial dysfunction and overt shock requiring ionotropic support were prominent clinical features and some developed coronary aneurysms, as well as macrophage activation syndrome (MAS). This inflammatory syndrome followed SARS-CoV-2 exposure or disease by several weeks. Soon thereafter, similar cases were reported from North America (4-6). Although it resembles KD, the severity of cardiovascular involvement and other non-overlapping features suggested that this may be a novel disease and was initially coined pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PMIS-TS) by the Royal College of Paediatric and Child Health in the UK (7), following the initial medical alert issued by the UK National Health Service. Names and case definitions have been issued by the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC) in the USA and European Centre for Disease Prevention and Control (8). Ultimately the name multisystem inflammatory syndrome in children (MIS-C) as agreed upon by the WHO and CDC. Common elements to all definitions are presence of prolonged fever, multi-organ dysfunction, and laboratory evidence of hyperinflammation. The CDC case definition includes age < 21 years of age, fever, laboratory evidence of inflammation, severe illness requiring hospitalization, multi-organ dysfunction (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological) without another cause together with evidence of current or recent SARS-CoV-2 infection(8).

Identifying features of MIS-C

In this volume of the *JCI*, investigators from two large pediatric centers report the clinical and immunologic features of their patients with MIS-C that help us gain insight into the pathogenesis of this inflammatory phenotype. Lee and Day-Lewis et al. (9) performed a retrospective study of 28 patients with MIS-C and compared them with historic cohorts of KD and MAS. While, Diorio et al. (10) prospectively studied patients with MIS-C (n = 6), severe COVID-19 (n = 9) and milder (hospitalized) COVID-19 (n = 5). Both performed studies to try to identify features of MIS-C that would aid in its diagnosis (9,10). As in previous reports, involvement of the cardiovascular, gastrointestinal and mucocutaneous systems were common in MIS-C with less prominent respiratory symptoms than in COVID-19. And that it is the cardiovascular features that are most dramatic in MIS-C and can lead to rapid decompensation. Myocardial dysfunction and/or shock was present in 53% and 83% (respectively), ionotropes were needed in 25% and 83% (respectively) and more than half required intensive care. In both cohorts, cardiovascular features overlapped with those of KD with 25% (7 out of 28) in Boston and 66 % (4 out of 6) in Philadelphia fulfilling criteria for complete or incomplete KD. And while most groups reported that the majority of MIS-C patients had been previously healthy, interestingly, two individuals with MIS-C from the Boston cohort had a past medical history of KD. Coronary artery involvement was detected in 7 of the 34 (20.6%) MIS-C patients reported in the two cohorts, which is lower than reports in the KD literature and lower than the 35% in the historic KD cohort. Treatment for MIS-C have been derived from lessons learned in KD and is reflected in the management plan in both cohorts; most children receiving IVIG and/or corticosteroids, with some receiving anakinra, an IL-1 cytokine blocking agent (9, 10). The clinical similarities and response to similar therapy opens the question as to whether this syndrome is a unique disease or part of the KD spectrum.

Environment triggered hyperinflammation

Kawasaki disease (KD) is thought to be an environment triggered inflammatory response leading to systemic vasculitis. KD is truly a syndrome, with a wide range of clinical phenotypes. The common clinical findings in affected children include the diagnostic criteria of prolonged fever (> 5 days) plus at least 4 of the 5 principle disease features including non-exudative conjunctival injection, mucosal erythema, redness/edema of the hands and feet, cervical adenopathy and rash (11). Cases of incomplete KD occur in which prolonged fever occurs with less than four clinical criteria plus presence of supportive laboratory findings. KD predominantly affects the medium sized arteries with a predilection toward the coronary arteries. Cardiac manifestations in KD include coronary aneurysm/dilatation, aortic root dilatation, myocarditis and cardiogenic shock (9). It predominantly affects young children and has a monophasic course for most. The disease manifestation are the results of an overly robust immune response, and while most agree on an environmental trigger, the exact agent(s) remain debated. One working hypothesis is that KD is initiated by an infectious trigger. This hypothesis is supported by both a seasonality of disease that varies by country and areas within countries and the occurrence of epidemics of KD (12, 13). Viruses including Corona virus infections have been implicated in KD pathogenesis(14, 15). In accord with this data, SARS-CoV-2 can be added to the long list of infectious agents associated with KD. Genetics have also been implicated as there are reports of affected sib-pairs, affected parent-child duos and racial differences with the highest prevalence in Asian children. Several susceptibility

genes have been implicated including immune related genes involved in T cell activation, B cell signaling, apoptosis and transforming growth factor beta signaling (13). Other environmental factors have also been implicated as there is an association with wind currents but not with particulate air pollution (16, 17).

Like KD, MIS-C is a syndrome complex with a wide spectrum of clinical phenotypes. A spectrum of COVID-19 associated hyperinflammation syndromes have been proposed (6) with three clinical patterns along the hyperinflammation spectrum in MIS-C: Shock, KD, and fever with inflammation. KD, like MIS-C, is an infection triggered hyperinflammatory syndrome with varying degrees of inflammation with cardiogenic shock and MAS at the severe end of the spectrum and a self-limited febrile illness at the mild end. So, although MIS-C resembles KD, the severity of cardiovascular involvement and other non-overlapping features have led to splitting this into a separate disease rather than lumping it into the Kawasaki syndrome disease spectrum. The severity of cardiovascular involvement with myocardial dysfunction and shock are features pointed to as distinguishing MIS-C as a unique disease process versus KD. However, KD can present with shock. In 2009, Kanegaye et al. (18) noted increasing number of patients at their center with acute KD presenting with shock and hypotension and defined this severe presentation as Kawasaki Disease Shock Syndrome (KDSS). In their cohort, nearly one third had myocardial dysfunction (EF < 54%), coronary artery abnormalities (62%) and were more likely to be resistant to IVIG(18). Subsequently, other groups reported similar presentations in their KD cohorts. A more robust immune response occurs in KDSS with higher blood inflammatory markers and one group reported significantly higher serum levels of IL-6, IL-10, INF-γ in their KDSS cohort (n=27) compared to KD controls (n = 43)(19). The incidence of shock in KD ranges from 1.4% to 7% of all KD cases (18, 20). The largest study to date reported 138 KD shock cases in 9,488 children with KD (1.5%) in Taiwan (21). Our own experience in Toronto shows an incidence of 2% for KD shock. An important characteristic of KD shock is the multiorgan nature of the inflammatory disease (22). The majority of patients with KD shock present with abdominal symptoms, mirroring predominant clinical features of MIS-C in children(23). Cardiovascular complications are dramatically increased in children with KD shock; 65% were found to have coronary aneurysm(24)

Life-threatening complications of KD, including KD shock and macrophage activation syndrome (MAS), have been considered rare events in the past, but like shock, MAS is reported in 2-5% of children with KD (25). MAS has also been reported with MIS-C. MAS is the result of a cytokine storm that can be occur in the setting of infection, rheumatologic disease and malignancy. Hyperferritinemia, cytopenias, liver dysfunction and coagulation abnormalities are common. Children with MAS are often treated with steroids, cytokine blocking agents (including IL-1 and IL-6 blockers), IVIG and in severe cases chemotherapeutic agents such as etoposide. Interestingly, children presenting on the severe KD spectrum with MAS and/or KD shock are usually older and are boys, consistent with the demographics described in MIS-C. Immunologically, many roads can lead to MAS, with the common underlying theme of hyperinflammation. In the case of MIS-C, SARS-CoV-2 infection triggered MAS is seen in both the acute infectious phase of disease and also in the post-infectious MIS-C phenotype.

Immunologic studies were done by both Lee and Day-Lewis et al. and Diori et al. groups to gain insight into pathophysiology of the disease as well as to explore their role as a biomarker to differentiate MIS-C from KD, MAS and COVID-19 infection. Elevation of the serum IL-6 and IL-10 was found in MIS-C patients in both cohorts as well as in severe COVID-19, whereas elevated IFN-γ was elevated across all 3 cohorts (mild and severe hospitalized COVID-19 and in MIS-C) in the Philadelphia cohort, but not as a prominent cytokine in the Boston MIS-C cohort. Diorio et al. reported that IL-10 plus TNF levels, RT-PCR viral cycle thresholds (Cts) and peripheral smear burr cells can help distinguished MIS-C from mild or severe COVID-19. While Lee and Day-Lewis et al. found that soluble IL-12, ferritin, IL-18 and CXCL9 elevations were higher in MAS compared to MIS-C (9,10). Blood vessels are thought to be an important target of SARS-CoV-2-triggered inflammation, mirroring the immunopathology identified in KD. The endothelial inflammation and injury described in COVID-19 (26) and in KD, is in accord with the findings of complement activation reported by the Philadelphia group.

Lumping or splitting

Characterizing the disease phenotype, both clinically and biologically, as described in the reports by Lee and Day-Lewis et al. and Diorio and colleagues, adds to the foundational work needed to better define this new syndrome. MIS-C came to attention with children presenting with dramatic and extreme clinical features, with the case definition reflecting the early observations based on children with severe disease, a circular and self-fulfilling definition. With further investigation and time, we are likely to learn about the milder end of the disease spectrum. Defining clear boundaries and differences between the newly named MIS-C hyperinflammatory spectrum of phenotypes from pre-COVID KD and/or the acute infectious phase of SARS-CoV-2 infection may be important for clinical management purposes - to target the invading virus during acute infection and/or the body's immune response. But from a pathobiology viewpoint, it may be a dis-service to fully appreciating the disease spectrum, as some of the differences may be due to the magnitude or kinetics of the immune response (Figure 1). The same excellent arguments in support of lumping or splitting are echoed in MIS-C, as in other infection triggered immune mediated diseases. The global pandemic has given us a unique opportunity to examine the immune response leading to the MIS-C/KD phenotype triggered by a single infectious agent simultaneously in multiple regions and genetic populations. Good-will and generosity has characterized the international community's response to COVID-19 and MIS-C is no exception. This silver-lining in the COVID-cloud will hopefully launch rigorous and scientific approaches to data collection and analyses using harmonized definitions to establish international disease registries, biorepositories and research programs to improve our understanding of this emerging syndrome.

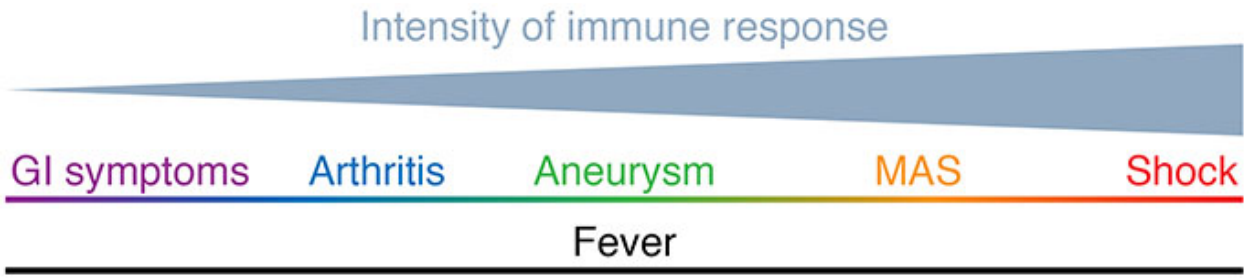

Figure 1: Heterogeneous spectrum of hyperinflammation in Kawasaki syndrome. Disease model proposes that the magnitude or kinetics of the immune response creates a continuum of the phenotypic severity in KD from mild organ involvement such as gastrointestinal symptoms (i.e., diarrhea, hydrops of the gallbladder (GB)) or arthritis, to severe life-threatening complications including MAS and cardiogenic shock.

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