

## Multisystem Inflammatory Syndrome Versus Kawasaki Disease: Potential Differences in Pathogenetic and Clinical Implications

To the Editor,

Multisystem inflammatory syndrome in children (MIS-C) has been suggested as a SARS-CoV-2-related proinflammatory condition that has a strong analogy to Kawasaki disease (KD), particularly in terms of its clinical findings.<sup>1,2</sup> The recently published report by Duman et al<sup>1</sup> has described an interesting case of acute myocardial infarction associated with MIS-C in a 9-year-old boy. In this regard, we would like to have further information on this interesting case and also make a few comments on potential differences between MIS-C and KD in the clinical setting:

First, both MIS-C and KD have been suggested to have an autoimmune basis.<sup>2-4</sup> On the other hand, while SARS-CoV-2 antigen has been proposed to induce the evolution of MIS-C,<sup>2</sup> the absolute causative agent still remains to be established in the setting of KD.<sup>2-4</sup> Interestingly, another strain of coronavirus [namely New Haven coronavirus (HCoV-NH)] was previously suggested to be associated with KD evolution.<sup>2,5</sup> Importantly, KD might also be emerge in children with a previous SARS-CoV-2 infection.<sup>2</sup> Notably, children with KD are generally younger (mostly infants and young children)<sup>3,4</sup> than those with MIS-C, potentially suggesting differential impact of age-related factors on the interaction between certain antigenic triggers and immune response.<sup>2</sup> Taken together, a recent SARS-CoV-2 infection (3-6 weeks earlier) most likely suggests MIS-C, particularly in relatively older children with specific clinical findings; yet this might not completely rule out a coincidental KD episode.<sup>2</sup> In this context, we wonder about the exact temporal and clinical details of SARS-CoV-2 exposure in the patient.<sup>1</sup> Was it just an asymptomatic exposure or an overt infection?

Second, both conditions present with persistent high-grade fever and involvement of various organ systems including cardiovascular (myocardium and coronary arteries) and gastrointestinal system along with mucosal and dermatological findings.<sup>1-4,6</sup> Importantly, serious myocardial involvement and the need for inotropic support (and admission to intensive care unit) might be more prevalent in the setting of MIS-C compared with KD.<sup>2</sup> We hold the opinion that the patient,<sup>1</sup> together with his coronary involvement, also had a "myocarditis component" (as consistent with left ventricular (LV) global hypokinesia and substantial troponin elevation). On the other hand, myocarditis in this context has been largely ascribed to "reversible myocardial stunning" associated with cytokine storm (rather than true myonecrosis).<sup>2</sup> Therefore, we wonder whether the LV systolic functions of the patient<sup>1</sup> improved on follow-up.

Third, the cytokine profiles might also have important implications in both conditions.<sup>2</sup> Serum levels of interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, and IL-18 were previously shown to be elevated in both conditions (mostly through activation of Toll-like receptors on endothelial cells with consequent activation of nuclear factor-kappa B).<sup>2</sup> However, activation of IL-17A pathway is exclusively encountered in the setting of KD.<sup>2</sup> Elevation of activated neutrophil count and serum cytokine

### LETTER TO THE EDITOR

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levels generally account for clinical and associated pathological findings (including necrotizing arteritis) in the setting of KD.<sup>3,4</sup> Notably, serum levels of IL-8 and IL-10 were previously reported to be higher in the setting of MIS-C compared with KD.<sup>2</sup> As an important outcome, IL-8 might potentially trigger a strong prothrombotic response.<sup>2</sup> Therefore, substantial hypercoagulation associated with IL-8, on top of coronary vasculitis, might have significantly contributed to the coronary occlusion in the patient.<sup>1</sup> This potentially suggests a higher risk of early thrombus formation in coronary arteries [even in the absence of coronary vasculitis or coronary artery aneurysm (CAA) formation] and veins in patients with MIS-C.<sup>2</sup> Accordingly, we wonder about the cytokine profile in the patient. Did the authors examine other vascular structures (cranial arteries, deep femoral veins, etc.) for potential thrombus formation in the patient?

Finally, coronary sequelae might arise as a significant challenge in both conditions.<sup>2-4,6,7</sup> Coronary vasculitis in KD might potentially end up with CAA formation and coronary stenosis, particularly in those who do not receive particular disease-modifying agents including intravenous immunoglobulin (IVIG) in a timely manner (within the first 10 days following fever onset) or in IVIG nonresponders.<sup>3,4,6,7</sup> Interestingly, patients with KD who are managed properly and have normal coronary arteries on initial coronary imaging might occasionally suffer from CAAs that attain their maximum size by about 6 weeks following disease onset.<sup>3,6</sup> These notions might also apply to patients with MIS-C despite the lower incidence of coronary sequelae in these patients.<sup>2</sup> Accordingly, did the authors perform serial coronary imaging on echocardiogram (following initial evaluation) in terms of CAA formation during the first few weeks? Even though the patient was managed in a timely manner (on the 5<sup>th</sup> day of fever), advanced imaging modalities (including computed tomography) performed around 6 weeks after

disease onset might be necessary to completely rule out any sequelae within the whole coronary arterial tree.

In summary, pathogenesis of MIS-C and KD seems to be different despite their similar findings.<sup>2</sup> Importantly, patients with MIS-C are more likely to have a rampant presentation (including hemodynamic compromise and arterial and venous thrombus formation).<sup>2</sup> On the other hand, long-term coronary sequelae, including CAA formation and coronary stenoses, have been more prevalent in patients with KD, potentially warranting lifelong surveillance.<sup>2-4,6,7</sup> However, further studies are still needed to explore particular aspects of both conditions.

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