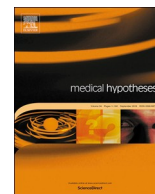




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Distinguishing between typical Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2

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ABSTRACT

In recent months, there are increasing reports of a Kawasaki disease-like syndrome in children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), termed 'Paediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV-2 (PIMS-TS)' in the UK. Debate is ongoing regarding the nature of these pro-inflammatory syndromes. We herein propose that the platelet count may, at least in part, be able to help us differentiate between the two aforementioned syndromes. In a recent report, compared to a historical 'classical' Kawasaki disease (KD) cohort, patients with PIMS-TS had significantly lower platelet counts (188 vs 383 g/L, $p < 0.0001$). A possible explanation for this is their difference in underlying immunopathogenesis. In KD, the fundamental pathogenesis is thought to be immune complex-mediated, hence, the use of intravenous immunoglobulin (IVIg) which competes with the immunoglobulin Fc receptors (FcRs) on inflammatory cells, preventing the activation of these cells and thereby ameliorating the inflammatory response. If left untreated, these immune complexes activates the inflammatory cells (including monocytes and neutrophils), which also results in recruitment of platelets, resulting in the thrombocytosis we commonly see in KD. These immune complexes may also bind to platelets directly via FcRs on platelet membranes. In contrast, in viral-associated hyperinflammatory syndromes (e.g. PIMS-TS or MIS-C), there are mediators being secreted in the process of eradication of the virus (mainly to stimulate CD8+ cells to kill viral infected cells), which would inadvertently suppress bone marrow function and activate platelets, culminating in thrombocytopenia.

Introduction

In recent months, there have been increasing reports of a Kawasaki disease-like, multisystem inflammatory syndrome in children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This has been termed 'Paediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV-2 (PIMS-TS)', in the UK, or 'Multisystem Inflammatory Syndrome in Children (MIS-C) associated with Coronavirus Disease 2019 (COVID-19)', in the US [1], although debate is still ongoing regarding the temporal association and nature of these hyper-inflammatory syndromes. It remains unclear whether they are distinct clinical entities, a result of SARS-COV-2 infection, or mere coincidences due to expected increases in the incidence of Kawasaki disease in the months of winter/spring [2].

Interestingly, Kawasaki disease is much more common in Asia compared to Europe or America, particularly in countries such as Japan and Korea [3]. In spite of this and the global distribution of COVID-19 cases, there has been no report of this unique inflammatory clinical

phenotype from China or Singapore hitherto [4].

At present, we know that PIMS-TS or MIS-C may present with variable clinical symptoms, including fever, diarrhoea and rash, making it hard to differentiate from other febrile illnesses and syndromes. As it is important to promptly recognise and treat these children who may deteriorate rapidly and require intensive care monitoring [1], we propose that an important distinguishing feature between a typical Kawasaki disease (KD) case and the current viral-associated hyperinflammatory syndrome is that of their platelet counts.

Hypothesis

A key distinguishing feature between a typical KD and the current viral-associated hyperinflammatory syndrome is that of their platelet counts.

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Evaluation of hypothesis

Although the variability for both MIS-C and early Kawasaki disease make clinically useful cutpoints unlikely, typical KD would have normal/high platelet counts [5,6] whereas the viral-associated hyper-inflammatory syndromes commonly present with lower platelet counts [7]. This concurs with the recent findings by Pouletty et al; compared to a historical 'classical' KD cohort, patients with PIMS-TS had significantly lower platelet counts (188 vs 383 g/L, $p < 0.0001$) [8]. This was also the case in two other brief reports of children with MIS-C [9,10]. In a series of six critically ill children with MIS-C by Chiotos et al. [9], the six children had initial platelet counts ranging from 46 to 217 (normal range: 150 to 400 $\times 10^3 /\mu\text{l}$). In a recent report by Kaushik et al. [10], which documented 33 children admitted to the pediatric intensive care units for MIS-C, the children had initial platelet counts ranging from 130.5 to 282 (normal range: 150 to 300 $\times 10^3 /\mu\text{l}$).

A possible explanation for this is their difference in underlying immunopathogenesis. In KD, the fundamental pathogenesis is thought to be immune complex-mediated, hence, the use of intravenous immunoglobulin (IVIg) which competes with the immunoglobulin Fc receptors (FcRs) on inflammatory cells, preventing the activation of these cells and thereby ameliorating the inflammatory response [11]. If left untreated, these immune complexes activates the inflammatory cells (including monocytes and neutrophils), which also results in recruitment of platelets, resulting in the thrombocytosis we commonly see in KD. These immune complexes may also bind to platelets directly via FcRs on platelet membranes [12].

In contrast, in viral-associated hyperinflammatory syndromes (e.g. PIMS-TS or MIS-C), there are mediators being secreted in the process of eradication of the virus (mainly to stimulate CD8+ cells to kill viral infected cells), which would inadvertently suppress bone marrow function and activate platelets, culminating in thrombocytopenia. Hence, we hypothesize that the platelet count may, at least in part, be able to help us differentiate the two aforementioned syndromes.

Conclusion

The COVID-19 pandemic continues to evolve and there are still many unknowns about the virus and undoubtedly limitations related to reporting a new, emerging pathogen in real time. Although this may be too early to generalize and further studies are necessary, it is hoped that prompt recognition of the appropriate inflammatory syndrome through the initial admission platelet counts may enable the timely administration of targeted therapy.

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Contributions

Wee Song Yeo conceived the original idea for the study. Qin Xiang

Ng and Wee Song Yeo carried out the study, and the relevant data analysis and interpretation. All authors contributed to the data analysis and interpretation. All authors discussed the results, contributed to the writing of the paper and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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