Response to: 'Exaggerated neutrophil extracellular trap formation in Kawasaki disease: a key phenomenon behind the outbreak in western countries?' by Yamashita *et al*

We read with interest the correspondence from Mizugishi *et al*.[1] The pathophysiology of Kawasaki disease (KD) and more recently Kawasaki-like paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or Kawa-COVID-19 remains largely unknown, even if the infectious trigger by SARS-CoV-2 in the prior weeks seems to be a key feature.[2] Furthermore, it is still uncertain whether Kawasaki-like PIMS-TS can be considered as the same entity as KD or if it should be individualised as a novel distinct condition, as it may have been suggested with several significant clinical and biological differences between classical KD and Kawa-COVID-19.[3]

Mizugishi *et al*[1] speculate that KD and Kawa-COVID-19 share a common pathophysiology through excessive neutrophil extracellular trap (NET) formation. Similar to Yoshida *et al*,[4] Mizugishi *et al*[1] showed increased NET formation in KD patients sera. Through a KD mouse model, the authors describe that severe vasculitis (in the aorta and coronary arteries) was associated with infiltrative neutrophils. Those neutrophils were primed to produce NETs through the PAD4 pathway and seemed to produce a specific type of NET formation (enriched in citrullinated histones). Excessive NET formation was also described in sera of adult COVID-19 patients with endothelial injuries. Kawa-COVID-19 could represent a severe form of KD triggered by an exaggerated NET formation induced by SARS-CoV-2.

NETs are an important first-line defence mechanism against bacterial, viral, fungal and parasitic infections, but they have been also suspected to play a role in autoimmune diseases such as systemic lupus erythematosus (SLE) or antineutrophil cytoplasmic antibodies-associated vasculitis (AAV) for example.[5] Van Dam *et al*[5] showed that NET formation is involved in the pathophysiology of two clinically and pathologically distinct forms of glomerulonephritis in AAV and SLE. The triggers and pathways leading to excessive NET formation in these renal autoimmune diseases are fundamentally different. Therefore, the elucidation of the disease-specific triggers of NET formation and the pathways that are involved is essential to understand the role of NETs and decipher their role in these different pathologies. Moreover, other pathways may be involved in SARS-CoV-2 postinflammatory diseases.

KD seasonality and peaks after viral outbreaks strongly suggest that KD is triggered by an infectious agent.[6 7] It has been shown that, compared with healthy control individuals, patients with KD have an altered Vβ T-cell repertoire (increased frequencies of circulating Vβ2+ and Vβ8.1+ T cells), leading to the hypothesis that a superantigen toxin might have a role in triggering KD.[8–11] The recent increase in KD-like patients after the SARS-CoV-2 outbreak (+497% increase (95% CI: 72 to 1082))[6] corroborates the hypothesis of a viral trigger in KD. Finally, Cheng *et al*[12] have recently found that SARS-CoV-2 encoded a superantigen motif near its S1/S2 cleavage site witch interacts with both the TCR and CD28,[13] resulting in massive production of proinflammatory cytokines including IFNγ, TNFα and IL-2 from T cells, as well as IL-1.[14] This cytokine storm leads to multiorgan tissue damage similar to what is now observed in PIMS-TS. Mice models and human tissue analysis have largely helped to better understand KD pathophysiology. In recent studies, it has been shown that neutrophilic infiltrations of the vessels were responsible for necrotising arthritis as well as other inflammatory mechanisms linked to the innate immune response and more broadly to the cytokine storm.[8]

As shown in our cohort,[3] the onset of the disease occurred 2–4 weeks after acute SARS-CoV-2 infection or exposure and the majority of patients presented no or low nasal SARS-CoV-2 viral loads (Ct >35 in 86%) and positive IgG antibodies, suggesting a postinfectious process. These results are in contrast to severe adult COVID-19 patients, where high viral loads were reported.[15] Thus, NET formation in these patients might be constitutionally different and linked to various pathways.

In conclusion, excessive NET formation seems to be an interesting lead to study and may help to better understand KD and more recently PIMS-TS. However, to better assess the link between KD and Kawa-COVID-19 and the potential role of SARS-CoV-2, NET formation response should be tested with serum from Kawa-COVID-19 patients and compared with classical KD patients and paediatric patients with mild SARS-CoV-2 infection, as a control group. To go further, this comparison should be stretched to severe versus non-severe Kawa-COVID-19 patients, as compared in our cohort, similar to the work of Mizugichi *et al*[1] in classical KD. Finally, larger studies seem necessary and should focus on NET formation molecules as well as morphology, kinetics, specific triggers, pathways and associated immune responses.

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