Good IgA bad IgG in SARS-CoV-2 infection?

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Dear Editor

Having read with interest the manuscript recently published by Zhao et al [1] we would like to comment on two points.

First, the authors respectively assayed all anti- SARS-CoV-2 antibodies in a double-sandwich method or specifically detected IgM and IgG. Of note, the first assay provided the best results, especially 100% positivity by day 8 in subjects with no viral RNA detectable any longer. The authors briefly suggest that this test also assessed IgA levels. This is corroborated by another recent study [2] where 92.7% of the subjects tested presented with anti- SARS-CoV-2 nuclear capsid IgA, while only 85.4% had IgM and 77.9% IgG. Data from both publications are consistent with what is known of mucosal immune responses, characterized first by the production of secretory IgA, systemic antibodies occurring later [3]. It is likely that SARS-CoV-2 behaves as other respiratory viruses [4], yielding the production of protective secretory IgA efficient in asymptomatic or mild infections. We suggest that it would thus perhaps prove interesting to investigate for the presence of such antibodies in the saliva of large cohorts of individuals to better appreciate the prevalence of this new infection.

The second point that we found intriguing is the relationship reported between high plasmatic total antibody levels and severe disease [1]. The authors merely propose this observation as a biomarker of severity, but also cite a publication by Liu et al. [5] of a model of SARS/CoV in macaques and of macrophage cultures with patient's serum samples. One may consider that high titers of antibodies could lead to their alveolar transudation and the formation of immune complexes (IC) with viral particles. Such IC would activate the complement system, which has been shown to play a role in lung injury in sepsis, through the activation of neutrophils [6]. Lung macrophages would also phagocytose such IC via Fc receptors and trigger the inflammatory responses of severe respiratory failure, especially in a context of anoxia [7]. However, elevated levels of TNFα, IL-6 but also IL-10 have been reported in severe cases [8]. It can thus be considered that after a pro-inflammatory phase, IgG-IC in the lower respiratory tract [3] induce the polarization of macrophages into type-2

non-inflammatory macrophages, producing IL-10, expressing PD-L1 and triggering regulatory T-cells (T-regs) [9]. Thus, an initially efficient (if somewhat overwhelming in severe cases) cellular immune response of anti-viral T-lymphocytes would be dampened by apoptosis through PD-1/PD-L1 interactions (partly explaining lymphopenia) and by an increase in T-regs. Other effects of transuding IgG would be antibody-dependent cellular cytotoxicity destroying the infected cells and causing lung damage. In the fragile anatomic environment of the lung, IC and the recruitment of polymorphonuclears could lead to vascular endothelium damage via an uncontrolled activation cascade translating in multiple organ failure with thromboembolic disorders leading to death [10]. We thus propose that a concomitant monitoring of anti-viral secretory IgA, IC and specific T cells could provide mechanistic insights in the pathophysiology of SARS-CoV-2 infection and provide prognostic and therapeutic guidelines.

None of the authors have any conflicts to disclose.

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