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Elevated interleukin-6, interleukin-10 and neutrophil : lymphocyte ratio as identifiers of severe coronavirus disease 2019

Nearly everyone is interested, having been taken unawares, by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the coronavirus currently causing a pandemic. The imminent emergence of an infective pandemic had been foreseen by viral ecologists such as Nathan Wolfe, who had actually proposed a coronavirus as the most likely candidate.[1] COVID-19 (coronavirus disease 2019) has become a household name in the last few weeks, each day seeing a frenzy of media coverage dominated by politicians; but scientists of all persuasions including immunologists, virologists, epidemiologists and clinicians have become engrossed by this disease. Although the disease only emerged last December, in the Chinese province of Wuhan, there have been hundreds of on-line reports and papers, the latter often deposited as pre-prints. There is a need now for consolidation of our knowledge-base on this virus, looking for themes and commonality from different studies around the world reported in peer-reviewed journals.

The manuscript published in this edition of *Immunology* by Tan et al.[2] is a timely and useful contribution to the COVID-19 literature. The authors analysed multiple cytokines and immune cell populations in the blood of patients admitted to Guangzhou Eighth People's Hospital in January and February 2020 who were infected with SARS-CoV-2. Considering this pandemic virus had only recently emerged, they managed to recruit 31 patients with clinically defined mild/moderate disease, 25 patients with severe disease and over 30 matched controls. Infection was confirmed by a swab/polymerase chain reaction, and the severity was taken from a clinical scoring system indicating the degree of respiratory compromise and/or shock. As the patients were admitted to hospital, a baseline blood sample was taken for flow cytometric analysis, bead-based multiplex assay for cytokines [interleukin-2 (IL-2), IL-4, IL-6, IL-10, tumour necrosis factor-α and interferon-γ] and leucocyte subset enumeration, measuring both relative proportions as well as absolute numbers (i.e. cells/μl). Key findings from this study include the observation that severe disease is clearly distinguished by a raised neutrophil count combined with a reduced lymphocyte count (hence a striking increase in the neutrophil : lymphocyte ratio), and an increase in IL-6 and IL-10 in the blood. Levels of C-reactive protein also increased markedly in severe disease.

Unfortunately, there were no outcome data on these patients, and no serial measurements over time; understanding early on which patients deteriorate, and identifying biomarkers, would enable heightened vigilance of these at-risk individuals. However, these results do point to interesting immunological findings: the lack of measured cytokines such as interferon-γ, tumour necrosis factor-α or IL-2 implies that T cells might play a more limited role in acute disease in many individuals. Even if the decrease in peripheral blood lymphocyte numbers reflects lymphocyte trafficking to infected organs such as the lungs, some increases in these cytokines might have been expected. Functional exhaustion of $CD8^+$ T cells, expressing NKG2A, has recently been reported in patients with SARS-CoV-2; this reverses with clinical recovery.[3] Similarly, a report from a different centre in China corroborates the lymphopenia for all subsets, which also corrects for patient recovery from COVID-19.[4]

The raised C-reactive protein, IL-6 and IL-10, along with neutrophilia, suggest that innate cells may be very important in the pathogenesis of severe disease. There has been much interest in IL-6, both as a marker of severity and as a speculative target for treatment with anti-IL-6 or anti-IL-6 receptor monoclonal antibodies. However, the role of IL-6 in these severely ill patients is still unclear: does it simply reflect a disease process that is out of control, or is it driving the disease end-organ damage? It is tempting to pursue IL-6-targeting treatment strategies, because in other situations, such as iatrogenic-induced cytokine storms, it can be highly effective.[5] However, IL-6 plays an important role in initiating anti-viral defences,[6] and understanding this balance is important to timing any interventions.

Many questions remain on SARS-CoV-2, including the relative roles of innate and adaptive immune responses; the nature of protective immunity; why it is essentially a disease of the elderly (children are almost disease free); and the mechanisms of pathology such as complement activation and angiopathies. Addressing these questions will allow targeted therapies to be implemented in controlled trials, whether this be vaccines for prevention or modulators of inflammation for treatment. This study by

Tan et al. is an important early addition to our understanding the pathogenesis of COVID-19.

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