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Assessing the entire landscape of antifungal immune response to COVID-19-associated pulmonary aspergillosis

Susceptibility to invasive pulmonary aspergillosis has been linked to myeloid cell dysfunction, and patients with neutropenia are particularly at risk for these infections. Recently, Simon Feys and colleagues showed in an Article published in *The Lancet Microbe* that the innate immune response to *Aspergillus fumigatus* is essential to fight against COVID-19-associated pulmonary aspergillosis (CAPA),¹ highlighting local quantitative and qualitative impairments in neutrophil functions.

However, other approaches for CAPA treatment should be considered because anti-*Aspergillus* immune response is now considered a continuum from innate to adaptive immune response. Besides the classically described myeloid response, other immune responses including NK cell-derived IFN- γ production and cytotoxic activity have been reported to be important against fungal infections.² Furthermore, the crosstalk between IgG-producing B1a cells and neutrophils is essential, with an antibody-dependent neutrophil-mediated host defence against *A. fumigatus* being profoundly affected by corticosteroid treatment.³ In addition, alterations of adaptive immune compartments, in particular T-cell exhaustion, are associated with severe fungal infections. PD-1 blockade in a murine model of post-sepsis aspergillosis has been shown to reinvigorate T cells and attenuate secondary aspergillosis.⁴

Altogether, these data suggest that abnormalities of the lymphoid compartments might considerably affect anti-*Aspergillus* response, which were not explored by Feys and colleagues. As part of a larger study of patients with COVID-19 with acute respiratory distress syndrome (ARDS) devoid of any immunosuppressive therapy (including

corticosteroids),⁵ we performed a longitudinal flow cytometry phenotypic analysis of peripheral blood cell subsets from five individuals with severe CAPA and eight with severe COVID-19 without aspergillosis, with 13 healthy volunteers as controls. In this limited but homogeneous cohort, patients with CAPA were characterised by a more profound lymphopenia (appendix p 1), together with stronger quantitative and qualitative alterations of lymphoid subsets compared with those without CAPA and healthy volunteers. Moreover, at days 1 and 4 after ARDS onset, T-cell counts were lower, and the expression of PD-1 exhaustion marker on these T cells was increased (appendix p 1). NK cell counts were not differentially affected in patients with COVID-19 with or without CAPA. Nonetheless, NK cell activation, as assessed by HLA-DR expression, was lower in patients with CAPA at day 7 after diagnosis of ARDS than in patients without CAPA and healthy volunteers (appendix p 1).

We believe that lymphocyte counts (NK cells and T cells) and markers of dysfunction of these cells are easy to measure in the blood. Thus, these markers should be considered for identifying critically ill COVID-19 individuals and those infected with influenza virus susceptible to *Aspergillus* infection.

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See Online for appendix