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LETTER TO THE EDITOR

Signals of T_h2 immune response from COVID-19 patients requiring intensive care

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Dear Editor,

Naïve T-helper cells (T_h0) can respond to novel pathogens that the immune system has never encountered before, as is the specific case of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the positive-sense single-stranded RNA virus responsible for the ongoing pandemic named coronavirus disease 2019 (COVID-19). Depending on the infectious agent, T_h0 polarize the immune response into T-helper type 1 (T_h1), the default response in immunocompetent subjects to intracellular or phagocytosable pathogens (e.g. viruses, bacteria, protozoa, fungi) and mediated by macrophages and T-cytotoxic (T_c) cells (*cell-mediated immunity*), or into T-helper type 2 (T_h2), classically directed against extracellular non-phagocytosable pathogens, for instance helminths, and whose main effectors are eosinophils, basophils and mastocytes, as well as B cells (*humoral immunity*) [1]. Eosinophils play a direct role in fighting RNA viruses, as demonstrated by the presence of RNases inside their granules [1]; however, they have been negatively associated with the pathophysiology of the respiratory virus infections, since they trigger bronchoconstriction and dyspnea, besides virus-induced exacerbations of allergic airways diseases, by releasing a large amount of cationic proteins and cytokines, among which interleukin-6 (IL-6), a key mediator also for the development of the "cytokine storm" in COVID-19 fatal cases [2, 3]. At some extent, the smooth muscle cells in the tunica media of blood vessels can produce IL-6, too [4]. It belongs to T_h2 cytokines class together with IL-4, IL-5, IL-9, IL-10, IL-13 and IL-25; contrariwise, IL-2, IL-12, interferon-γ and tumor necrosis factor-α are the main T_h1 cytokines, able to stimulate the inducible form of the nitric oxide (NO) synthase to produce NO free radicals endowed with virucidal activity [1]. To minimize the contagion risk in healthcare personnel, we have prepared and examined a limited number of 15 peripheral blood smears from a wider series of hospitalized COVID-19 patients, just admitted to intensive care and monitored through blood tests; in all the cases, we have found cytological signals of T_h2 immune response, represented by eosinophilia plus basophilia, degranulated eosinophils, Türk cells or plasma cells, together with rouleaux and T_c lymphopenia (Fig. 1). On the basis of our findings, for reasons still unclear, maybe related to the viral load, T_h1 and T_c breakdown, antigenic cross-reactivity or the type of antigen-presenting cell stimulating T_h0, the immune system mounts a T_h2 response against SARS-CoV-2 in patients requiring intensive care, rather than a T_h1 response, which would keep the infection under control by means of macrophages and T_c cells. This event is more likely in patients affected by cancer, immunodeficiency, autoimmune disorders, congestive heart failure, chronic obstructive pulmonary disease and hepatic cirrhosis, or in those who have suffered major surgery and traumatic injury, or who are on glucocorticoid therapy and total parenteral nutrition, all known conditions suppressive to T_h1 immunity [1]. The mounting of a T_h2 immune response allows to explain well the concurrent

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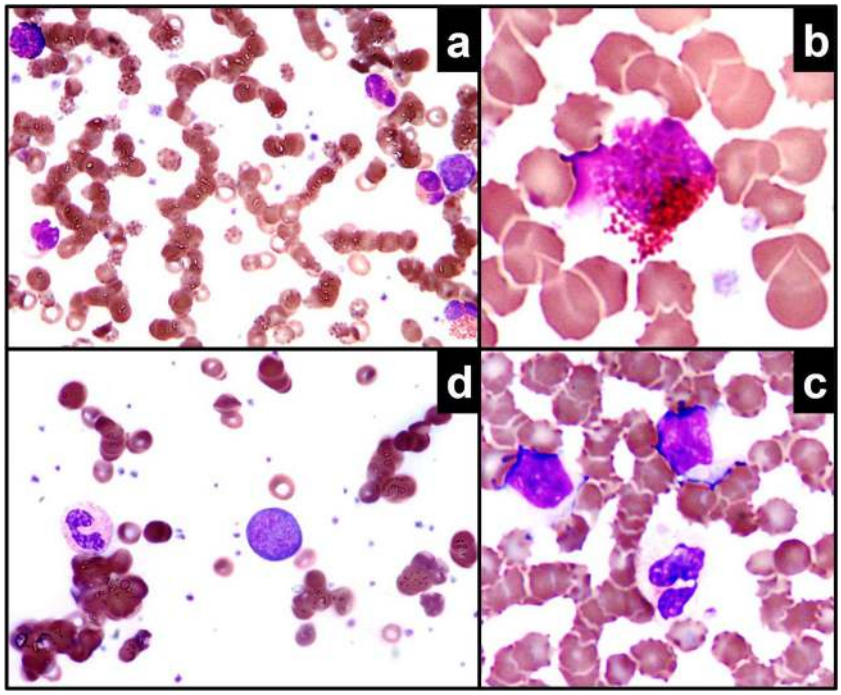

Fig. 1 Cytological signals of T_h2 immune response on peripheral blood smears from COVID-19 patients requiring intensive care: **a** on the right side of the panel, three eosinophils in a row accompanied by a basophile in the upper left corner (× 40 objective); **b** an eosinophil in the degranulation phase (× 100 objective); **c** a bilobed degranulated eosinophil in the center of the panel (× 100 objective); **d** an immature plasma cell (Türk cell) in the midst of prominent rouleaux (× 100 objective) (May-Grünwald stain)

gastrointestinal symptoms present up to 30% of COVID-19 patients and significantly associated with dyspnea [5]; in fact, hyperperistalsis and gastric fluid acidification are also two notorious default mechanisms of defense to expel parasites governed by T_h2 cytokines [1].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures followed were in accordance with the ethical standards and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Not applicable since the manuscript does not contain any patient data.

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