General correspondence

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COVID-19: where have the lymphocytes gone?

One of the predominant features of coronavirus disease 2019 (COVID-19) is absolute lymphopenia, which is relevant in clinical phases immediately preceding the deterioration of respiratory function and the need for oxygen supply or assisted ventilation.[1] Homing or chemiotaxis phenomena should help to understand the possible pathogenetic significance of lymphopenia, perhaps as a sign of incipient interstitial lymphocytic pneumonia. Interestingly, in Severe Acute Respiratory Syndrome (SARS) animal models, lung inflammation intensified after viral clearance, with a peak around 14 days after infection.[1,2] Similar observations have been made in SARS patients, raising the question of whether the damage could be caused by uncontrolled viral replication or uncontrolled immune responses.[1,2]

Postmortem biopsies in COVID-19 subjects indicate that in early stages a lymphocytic alveolar or interstitial pattern is observed, giving way later to acute fibrinous organising pneumonia culminating in diffuse alveolar damage.[3–5]

In light of these findings, we speculated that steroids with prominent lympholytic activity, such as high-dose dexamethasone, could be useful in decreasing the clinical manifestations and severity of interstitial pneumonia if administered within the time frame of incipient and evolving lymphopenia, that is, before the onset of respiratory function deterioration. We administered high-dose dexamethasone to 79 patients (Table 1), who accounted for 39.2% of cases in our hospital from 22 February to 11 March 2020, before individualising steroid treatment following the World Health Organization recommendation.[6] Steroid treatment was usually administered along with antiretrovirals; no antibiotics were given except in cases of procalcitonin increase.

As the data on autopsy findings in COVID-19 are scarce, the main question remains: where did the lymphocytes go? If there is no lymphocytic interstitial pneumonia, then there is no reason to investigate homing or chemiotaxis phenomena. In a study based on postmortem core biopsies, where the time from disease onset to death ranged 15–52 days, all patients had lymphocytopenia, except for one patient with leukaemia.[4] In patients with lymphocytopenia, postmortem histology showed diffuse alveolar damage with injury to the alveolar epithelial cells, hyaline membrane formation, and hyperplasia of type II pneumocytes. In another study with two autopsies, diffuse alveolar damage and airway inflammation suggested a true virus-related pathology.[5] If it is true that there are many endothelial cells in the bloodstream, it is unclear why there are macrophages and no lymphocytes in the interstitium.

SARS-CoV-2 is a deceptive virus, and COVID-19 is a deceptive disease. The immunological key to understanding many of its clinical features may well be the lymphopenia. As a next step in research, it is important to find out where the deceptive journey of lymphocytes is. Is there a systemic or virological reason for lymphopenia?

Table 1 Clinical outcomes in COVID-19 patients treated with steroids (S/s)

Outcomes in the steroid group	
Total (steroid)	201 (79)
Male/female	63/16
Median age (range) (years)	59 (33–87)
No. survivors (%)	71 (89.8)
Death within 7 days from S/s onset	4 (5.0)
Death within 14 days from S/s onset	0 (0)
Death within 28 days from S/s onset	4 (5.0)

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