Extended Abstract

Correlation between thymic output and disease severity in critically ill COVID-19 patients: extended abstract

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Introduction

COVID-19 is a very concerning pathology with heterogeneous manifestations going from flu-like syndrome to acute respiratory distress syndrome. The emergence of new viral variants presenting higher transmission rates is of major concern but to date the infection fatality rate is still mainly determined by the age of the patients and their comorbidities (1,2). Thus, improving patients' stratification is a major concern in clinical practice nowadays. To this aim, the identification of new prognosis factors could be helpful. In that way, several studies have identified clinical and biological risk factors for SARS-Cov2 infection related death, which include age, gender, co-morbidities (such as obesity, diabetes, hypertension), D-dimer concentration (3), low lymphocyte counts and high C-reactive protein(1,2,4,5). Also, recent investigations have highlighted the role of increased plasma concentration of pro-inflammatory cytokines (cytokine storm) (6,7), impaired type I interferon responses (8), profoundly altered T cell phenotypes and functional exhaustion of antiviral lymphocytes in the severity of COVID (9-11). These findings suggest an ineffective immune response associated with a pathogenic dysregulated inflammation (5,11,12).

In adults, thymic involution is associated with age. Thymus hyperplasia, associated with thymus hyperactivity, is quite unusual but has been described in auto immune diseases and, interestingly, in reaction to profound lymphopenia associated with acute viral infections (13). Accordingly, studying thymic function in hospitalized COVID-19 patients could be relevant to specify its importance in the pathology and identify a new marker for disease outcome.

Thymic activity can be evaluated through quantification of T cell receptor excision circles (TRECs) (14), circular DNA molecules which are excised from the T cell receptor alpha and beta (TCRA and TCRB) loci during TCR rearrangement. Circulating TREC frequencies correlate with thymic size and activity and decrease with age. Different types of TRECs are generated during thymocyte differentiation: DJβTRECs (byproducts of TCRB rearrangement) are generated early on during thymocyte development while the sjTREC (byproduct of TCRA rearrangement) is produced later on. Between these 2 recombination events, the thymocytes extensively proliferate leading to increased thymic export and to the dilution of the DJβTRECs. Indeed, TRECs are not duplicated during cell division, their frequencies in a T-cell population are thus inversely proportional to its proliferation history. Moreover, in lymphopenic patients (including COVID-19), compensatory proliferation of peripheral naive T cells further dilutes TREC molecules. Accordingly, the sj/βTRECs ratio which measures intra-thymic proliferation and does not depend upon peripheral naïve T-cell proliferation or survival, directly reflects thymic output (14). This tool is thus more precise to evaluate thymic output than direct quantification of the sjTREC frequency.

Objectives

The main objective of this study was to determine whether thymus hyperplasia and/or hyperactivity could be associated with disease severity and to determine if thymus enlargement could be predictive of patient outcomes.

Moreover, we assessed the circulating levels of cytokines in patients hospitalized in intensive care unit (ICU) for COVID-19 as compared to patients hospitalized in the same ICU for other pathologies and established correlates between cytokines levels and COVID-19 severity.

Material and methods

Fifty adult patients, admitted in ICU at the Clinique Ambroise Paré (Neuilly; France) between March and April 2020 for COVID-19 pneumopathy, with SARS-CoV-2 infection confirmed by nasal viral RNA detection were recruited for this study and followed up until complete recovery or death. Similarly, 37 patients hospitalized for non-COVID-19-related pathologies in the same ICU during the same period were recruited as controls. Most of them were hospitalized for planned cardiac surgery. All the patients were included after a written informed consent.

Disease severity and thymus size were assessed using CT-scan imaging. Parenchymal window was analyzed and a score was attributed to each patient from 0 in absence of pulmonary alteration to 6 in case of pulmonary fibrosis. Specific settings were used to examine the thymus area and a score from 0 to 7 was attributed. To decrease the variability, we decided to consider 3 categories 0, A or B to define patients with fatty thymus atrophy, patients with very moderate infiltration of thymus area and patients with significant thymus hyperplasia, respectively. All images were independently reviewed and classified by two radiologists.

TRECs frequencies were quantified through real time quantitative PCR performed on purified peripheral blood mononuclear cells with LightCycler technology (Roche). The sj/βTRECs ratio was then calculated for each sample (14).

Plasma concentration of 33 cytokines was quantified using a multiplex ELISA (U-plex Meso-Scale Discovery).

Results

Thymus enlargement, as evidenced by thoracic CT scan, was evidenced in the group of COVID-19 patients, especially in individuals under 80 years old, as compared to patients from the control group. Interestingly, thymus hyperplasia was associated with more extensive lung injury score on CT-scans (P=0.01), but with a lower mortality rate (P<0.001).

Moreover, the sj/βTRECs ratio, which reflects thymic activity, was correlated in our cohort with the size of the thymus as defined by CT-scan thymic score. This result suggests that thymus enlargement was biologically associated with enhanced thymic function.

Finally, among the 23 cytokines tested, we evidenced an enhanced expression of IL-6, IL-10 and MIP1α in severe COVID-19 patients. Interestingly, the plasma levels of these cytokines correlate with disease severity (P=0.024, 0.056 and 0.019, respectively) which is consistent with previous reports (6,7,9). Moreover, we demonstrated higher IL-7 plasma concentrations in COVID-19 patients than in controls (P=0.038).

This is of particular importance as IL-7 is known to participate in the initiation of antiviral immune responses (15) during acute mucosal infections (16,17) and is a critical cytokine for the survival and the differentiation of immature thymocytes (18).

Discussion

Altogether, these data suggest that the thymus could play a crucial role in response to SARS-CoV-2 infection. Thymic hyperplasia, as a consequence of IL-7 overexpression in response to viral infection (danger signal) and/or to virus-induced lymphopenia (homeostatic signal), leads to enhanced thymic production and is associated with improved clinical outcome in severe COVID-19 patients. The lack of thymic activity/reactivation in older SARS-CoV-2 infected patients could contribute to a worse prognosis (19).

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