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Clinic Value Analysis of Combined Detection of White Blood Cells and T-cell Subgroups in a Patient with SARS-CoV-2 Infection

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Abstract To analyze and assess the changes of peripheral blood cells of a patient with SARS-CoV-2 infection, we collected and retrospectively analyzed the white blood cells, T-cell subgroups and interleukin 6 (IL-6) of a patient with COVID-19. Compared to the corresponding normal range, the percent of eosinophiles (ESO%) and count of EOS decreased; the percent of T-cell subgroup with double negative for cluster of differentiation 4 and 8 ($CD4^-CD8^-$ T%) increased. The concentration of IL-6 was 21.5 pg/ml, which far exceeded the normal range (0-3.4 pg/ml). These results indicated that some indices of peripheral blood cells could be taken as reference parameters to assess the infection or severity of SARS-CoV-2.

Keywords: *COVID-19, IL-6, Lymphocyte, SARS-CoV-2, T-cell subgroup*

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1. Introduction

Currently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread hundred of countries outside China and made millions of people infected and more than two hundred thousands of death. [1] The effect of SARS-CoV-2 infection on lymphocyte has reported in several references. [2,3] So far the decrease of lymphocytes or lymphopenia was generally considered being relative to the novel coronavirus infection. [2,3] In this study, we observed a case with coronavirus disease 2019 (COVID-19), analyzed the changes of peripheral blood cells and preliminarily assessed the significance of the indices for diagnosing and treating COVID-19.

2. Patient Report

A 34-year-old man presented with fever and being mild short of breath for 4 days and admitted to the clinic of Infectious Disease Department of Affiliated Hospital of Jining Medical University, Jining City, Shandong Provice, China. He tested negative for the common respiratory pathogens, including respiratory syncytial virus, adenovirus, Mycoplasma pneumoniae, Chlamydia pneumoniae. CT showed multiple regions of patchy consolidation and ground-glass opacities with indistinct border in both lungs. Meantime, the results for successive twice SARS-CoV-2 RNA assay were positive.

We performed a retrospective study. Blood routine and lymphocyte subtype were detected with cell analyzer and flow cytometer, respectively. Interleukin 6 (IL-6) was also detected with enzyme linked immunosorbent assay. The results were collected and analyzed comparing to the reference ranges.

The results of White Blood cell (WBC) and T-cell subgroups were listed in Table 1.

As Table 1 showed, the percent of eosinophiles (ESO%) and EOScount were lower than the corresponding reference range; the counts of monocytes (MON) were higher than the normal range. The percent of T-cell subgroup with double negative for cluster of differentiation 4 and 8 ($CD4^-CD8^-$ T%) was 6.42% which was slighly lower thanf the upper-limit of the reference range. The concentration of IL-6 was 21.5 pg/ml and the vlaue was far exceeded the normal range.

Table 1. Laboratory results for peripheral lymphocytes and T-cell subgroups

Indices	Ref. ranges	Results
LEU, 10^9/L	3.5-9.5	9.40
LYM%	20-50	34.90
MON%	3-10	9.50
NEU%	40-75	55.50
EOS%	0.4-8	0.10
BAS%	0-1	0.00
LYM, 10^9/L	1.1-3.2	3.27
MON, 10^9/L	0.1-0.6	0.89
NEU, 10^9/L	1.8-6.3	5.19
EOS, 10^9/L	0.02-0.52	0.01
BAS, 10^9/L	0-0.1	0.00
TT%	50-80	80.78
NK%	7-40	6.82
TB%	5-18	12.31
Th%	27-51	43.05
Ts%	15-44	31.08
Th/Ts	0.71-2.78	1.39
NKT%	2.48-11.28	5.67
$CD^{3+}CD4^+CD8^+$ T%	0-3	0.03
$CD3^+CD4^-CD8^-$ T%	0-6	6.42
IL-6, pg/ml	0-3.4	21.5

LEU, leukocyte; LYM & LYM%, count and percent of lymphocytes; MON & MON% , count and percent of monocytes; NEUY & NEU%, count and percent of neutrophiles; EOS & EOS%, count and percent of eosinophiles; BAS & BAS%, count and percent of basophiles; TT%, percent of total T lymphocytes; NK%, percent of natural killer cells; TB%, percent of total B lymphocytes; Th%, percent of helper T cells with double positive for cluster of differentiation 3 and 4 ; Ts%, percent of suppressor T cells with double positive for cluster of differentiation 3 and 8; Th/Ts, ratio of Th versus Ts; NKT%, percent of neutral killer T cells; $CD4^+CD8^+$ T%, percent of T subgroup with double positive for cluster of differentiation 4 and 8; $CD4^-CD8^-$ T%, percent of T subgroup with double negative for cluster of differentiation 4 and 8; IL-6, interleukin 6.

3. Discussion

In this study, the total number of WBC, the counts and percentages of neutrophiles, monocytes and basophiles were all normal. Generally, ESO is used to diagnose allergic diseases and seldom used to estimate virus infection. Interestingly, we found that the count of ESO and ESO% were all below their reference ranges in the present study. This results were similar to a report, in which Li and colleagues [4] found the count of EOS of the patients with COVID-19 was statistically higher than that of patients with virus pneumonia of non-COVID-19, who tested positive for the repiratory viures including Coxsackie virus, Herps Simplex vurus, respiratory syncytial virus, Incluenza A and B virus. In another report, the scientists investigated 140 cases with COVID-19 and found 52.9% of the patients had eosinopenia, and moreover, the absolute numbers of circulating eosinophils correlated positively with the numbers of lymphocytes for all patients. [2] As to the mechanism for this decline, one opinion considered that more adrenocorticotropin would be secreted on the condition of virus infection; [4] another opinion thought the reason probably lie in immune system which was attacked by SARS-CoV-2. [5] However, whether these two aspects of factors simultaneously cause the decrease of ESO count needs to be proved with more studies in future.

Lymphocyte detection is considered as an index which is closely related to COVID-19. Some scholars reported that the percent or absolute value of lymphocytes generally declined, and the decline rate even to more than 69%. [2,3] In Huang's and Wang's studies, up to half of the patients had lymphopenia. [4,6,7] Besides, the decrease of lymphocytes was related to the severity of the infectious disease. In Zhang's report, [8] the research results showed that when lymphocytes count $<0.4 \times 10^9$/L, 81.8% of the COVID-19 patients were severe cases; when the percent of lymphocytes <10%, 81.3% of the patients were severe cases. So they considered that both of lower lymphocyte count and percentage were strongly related to severe 2019 novel coronavirus pneumonia and composite endpoint. [8] In our study, LYM% of this patient was in normal range, but the absolute number of lymphocytes slightly exceeded the upper limit. The possible reason for such a phenomenon was that the infection for the patient was at the early stage, and lymphocytes increased to eliminate the causative pathogen under the stimulation of the virus. [9] Subsequently, the lymphocytes numbers would decline along with the progress of COVID-19, especially when the pneumonia developed into severe or critical severe phase. [2,10] Presently, it is clear that lymphopenia could be used as a reference index in diagnosis of the novel coronavirus infection in clinic, [11] and even can be taken as a predictive diagnosis factor to predict disease severity of COVID-19. [12]

The reasons for lymphocytes decrease of COVID-19 patients is still unclear so far. Some researchers thought that the immune cells consumption and the immune function inhibition caused by SARS-CoV-2 were the main reasons. [13] A current study showed that the negative function of lymphopenia to COVID-19 was associated to cytokine release syndrome, and this indicated that the broken homeostasis of immune system probably was the radical cause for the deterioration of COVID-19 pneumonia. [14] In this study, we detected the T-cell subgroup and found that the percent of NK slightly decreased. This finding was just consistent with Shi's report in which the innate immune was activated and exhausted to some extent at the early stage of COVID-19. [9] In another study, Zheng et al. [15] showed the total number of NK and $CD8^+$ T cells decreased markedly in patients with SARS-CoV-2 infection. This finding again proved that NK was one of the important cells fought against SARS-CoV-2 infection; meantime, $CD8^+$ T cells also played an important role in this protective function.

As an adaptive immune index, the percent of $CD3^+CD4^-CD8^-$ T cells was detected in our study. As everyone knows, $CD3^+CD4^-CD8^-$ T cell is a subset of regulatory T cells (Treg), which performs negative regulation in many diseases. It's elevation probably showed that the down-regulation of immune system has been activated to prevent from too strong immune response at the early infectious stage. This response of cell immune system like a two edges of sword, because SARS-CoV-2 began to break down antiviral immunity at the early stage of infection. [16] However, as Table 1 showed, the adaptive immune system, such as Th, Ts,

NKT, etc, was kept in a normal range, and this possibly was due to the negative regulation of $CD3^+CD4^-CD8^-$ T cells. Compared to the patients who were in early phase of or with mild symptom, T cell immune always turns to disorder in those patients at later stage or with severe symptom, and $CD4^+$T, $CD8^+$T, B cell and NK cell counts were often above normal. [17] Along with deteriorating progress of COVID-19, the count or percentage of the lymphocytes subsets of the patients would continuously decline, until death. [17]

In the researches of pathogenic mechanism related to SARS-CoV-2, cytokine storm places an important role and is taken as one of the fatal factors for the severity of COVID-19. [14,18] Huang et al. [14] found that there was out of balance between Th1 and Th2 lymphocyte. The levels of inflammatory cytokines mainly secreted by Th1 lymphocyte highly increased, and which had a positive relation to severity of COVID-19. In this study, we detected the inflammatory IL-6 and found it's concentration was high to 21.5 pg/ml which was much higher than the upper normal range. This result was consistent to the reports of Wan [17] and Liu [19]. Increase of IL-6 indicated the immune respond mediated by T lymphocyte for COVID-19 patient. In Chen's report, [3] elevated IL-6 was related to the severity of COVID-19, and the higher the level of IL-6 was, the severer the infectious disease became. For the severe or critical severe patients with COVID-19, the changes that IL-6 increase while T cell subset decrease probably show that T lymphocytes are excessively activated. [5,18] This probably is the root reason for the bad outcome and even death for the patients with SARS-CoV-2 infection or COVID-19.

In generally, detection of peripheral blood cells and T lymphocyte subsets is necessary for diagnosis of COVID-19, and some indices of them even can be used as reference parameter to assess the severity and treatment of the disease. Besides, for clinicians and science researchers, the cellular immunity of COVID-19 patients should be paid more attention to and considered as an therapeutic target through regulating immune unbalance.

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