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Article

The effect of COVID-19 infection on the white blood cell count and lymphocyte proliferation activity at the early stage of the disease

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Abstract
Since the appearance of COVID-19 at the end of December 2019 in Wuhan, China, and its prevalence in many countries, the symptoms of this disease extended from respiratory problems to a wide range of symptoms associated with the invasion of the virus to many organs and tissues in the body of patients. The white blood cells, particularly T lymphocytes, are the main effectors in defense against viral infections. This study was performed to investigate the response of white blood cells to the infection of SARS-COV-2 at the early stage of the disease. T cells decreased in number in the circulation, but this decrease was not associated with an impairment of their activity. Moreover, stimulation of virus-infected T cells with non-specific mitogen revealed increased cell proliferation. This study concluded that T lymphocytes are highly activated during SARS-COV-2 infection, despite lymphopenia, at least at the early stages of the disease.

Keywords: COVID-19, lymphocyte proliferation, mitotic index

Introduction

In December 2019, hospitals in Wuhan, China, reported a cluster of cases of pneumonia with an unknown cause, attracting national and international attention[1]. The disease was coined COVID-19.

Based on genome characteristics, SARS-CoV-2 is accused as the causative pathogen of COVID-19, which has been identified as the seventh type of coronavirus to infect humans2. COVID-19 symptoms include fever, cough, hypoxia, and fatigue, as well as sputum production, headache, diarrhea, dyspnea, and lymphopenia3.

The most influenced organ of an infected person due to coronavirus is the lungs in severe cases. SARS-COV-2 was found to attach to the Angiotensin-converting enzyme 2 (ACE2) receptor, which is the most abundant in type II alveolar cells of the lungs where the breathing process's gas exchange occurs4.

Viruses are released in respiratory excretions by an infected person when he or she coughs, sneezes, droplets that rarely travel more than six feet, or talk and infect anyone if they come into direct contact with the mucous membrane. Infection can also occur when someone touches his eyes, nose, or mouth after contacting a contaminated surface5.

Several biological abnormalities found in most COVID-19 patients, such as leukopenia and lymphopenia, make complete blood count (CBC) a potential aid in diagnosing COVID-19 [6].

A SARS-CoV-2 infection can start a good immune response, which involves immune activation with antiviral immune responses via T helper cells (Th) cytotoxic

T cells (CTLs) and stimulate infected cell killing. The transition between innate and adaptive immune responses is critical in determining the disease progression. Early immune responses are primarily protective. However, dysregulated and poor inflammatory responses can fail to remove viruses and result in poor clinical outcomes7. Lymphopenia observed in COVID-19 patients, may occur as a result of Infiltration of lymphocytes into the lungs. Significant and rapid reductions in lymphocyte counts may play a role in the pathophysiology of COVID-19 and contribute to its development to severe COVID-19. Notably, in severe COVID-19 individuals, the numbers of regulatory T cells were lower than in mild cases**8.** Lymphocytic proliferation assay is a commonly used method for determining lymphocyte function. PHA is a potent mitogen that promotes T-cell activation and proliferation regardless of antigenic specificity9. Much research has been conducted to study the response of cellular immunity in COVID-19 patients in severe conditions with a wide range of symptoms.

This study aimed to assess the effects of SARS-COV-2 infection on the activity and proliferation ability of T cells in COVID-19 patients at the early stages of infection since these cells are the key factor for the development of immunity or progression to more severe disease. The response amount of the patient's T-cells to the mitogen indicates the competence of cellular immunity.

Subjects: Twenty-two patients were admitted to the Isolation center of Baghdad Teaching Hospital with corona-like symptoms of less than one week and confirmed by PCR assay for nasopharyngeal samples as recent infection with COVID-19. This group of patients was tested for complete blood count and T lymphocyte proliferation assay against an equal number of healthy control groups (neither infected nor vaccinated against SARS-CoV-2). The two groups were nearly equal in their ages and gender distribution.

Materials and Methods

Blood samples

Five milliliters of venous blood were withdrawn from each subject by vein-puncture under an aseptic condition by disposable syringe. The blood samples were divided into two parts; two milliliters of the peripheral venous blood were dispensed in a test tube containing K3 Ethylene Di-amine Tetra-acetic Acid (K3EDTA) for testing complete blood count, and two ml of the blood sample was dispensed in a test tube contains Lithium Heparin (1 ml blood: 20 ul heparin) for RPMI 1640 culture.

Complete Blood Count Assay was done by hematology analyzer Mindray BC -5000

T lymphocytes Mitotic index Assay

1. Procedure

The procedure used by the Iraqi Center for Genetics and Cancer Research and modified by Abbas Arrak (10) was followed:

1) 0.3 ml of heparinized blood was inoculated into two venoject tubes containing 4 ml of culture medium for each. 0.3ml of PHA (Capricorn Scientific GmbH) was added to one of them and labeled as (with PHA); the other tube was not treated with PHA and labeled as (without PHA).

2) The tubes were incubated at 37C for 72 hrs with gentle shaking twice daily.

3) The cultures were transferred to centrifuge tubes and spinned at 1500 rpm for 10 min.

4) The supernatant was discarded and 10ml of pre-warmed (0.075 M) KCl was added and mixed thoroughly.

5) The tubes were incubated at 37C for 50 min.

6) The tubes were centrifuged at 1500 rpm for 10 min. and the supernatant was discarded.

7) 5 ml of freshly prepared fixative (3 parts of methanol (Haymankimia, UK) to 1 part of acetic acid (Avonchen limited) was added, drop by drop and shaked gently.

8) Steps 6 and 7 were repeated at least twice more.

9) The tubes were spinned at 1500 rpm for 10 min.

10) The Cells pellet was resuspended in a small volume of fresh fixative and dropped (from about 50 cm height) onto a highly-cleaned microscopic slide and allowed to dry in the air.

11) Slides were stained for 15 min. with Giemsa's stain, washed with tap water, dried, and examined for lymphoblast cells.

12) At least 500 cells were counted and the result was recorded as:

$$\text{Mitotic index} = \frac{\text{No. of Lymphoblast}}{\text{Total no. of lymphocytes counted}} \times 100$$

Statistical analyses: Statistical Package for the Social Sciences (spss) version 26 was used in this study. Descriptive statistics including minimum, maximum, mean, and standard deviation for each parameter tested were done for the two groups (COVID-19 patients and healthy control). The t-test did the significance of differences between the two groups for each parameter tested for equality of means.

Results

A. Effect of COVID-19 infection on lymphocyte proliferation.

Twenty-two COVID-19 patients were tested for complete blood count and T lymphocyte proliferation assay against an equal number of healthy controls (noninfected nor vaccinated against SARS-CoV-2). The two groups were nearly equal in their ages and gender distribution. Table 1 reveals the results of WBC count (total and differential) and the number of lymphoblasts before and after treatment with PHA, as well as the mitotic indices of the proliferated lymphocytes for the healthy control group.

parameter	Minimum	Maximum	Mean	Std. Deviation
Age (years)	10.00	51.00	23.954	10.485
WBCs count (total)	4.40 (x1o^3)	19.50 (x1o^3)	8.50 (x1o^3)	3.232
Neutrophiles (%)	45.50	72.40	60.52	7.359
Lymphocytes (%)	20.70	43.50	31.70	6.348
Monocytes (%)	3.10	8.70	5.64	1.444
Esinophiles (%)	0.40	4.60	1.80	1.119
Basophils (%)	0.40	3.60	0.87	0.650
PHA treated lymphocytes	243.00	442.00	342.86	54.129
Non treated lymphocytes	132.00	238.00	176.72	28.525
Difference between treated and non-treated lymphocytes	65.00	299.00	166.13	59.047
Mitotic index of treated lymphocytes	48.60	88.40	68.57	10.825
Mitotic index of non-treated lymphocytes	26.40	47.60	35.34	5.705
Mitotic index of difference between treated and non-treated lymphocytes	13.00	59.80	33.24	11.821

Table 1. Descriptive statistics of tested parameters for the healthy control group.

For the healthy control group, out of 500 lymphocytes counted, 132-238 cells, the mean was 176.7 cells were transferred to lymphoblasts without PHA treatment. 243-442 cells, the mean was 342.8 cells were transferred to lymphoblasts after treatment with PHA. The difference in cell numbers before and after treatment ranged between 65-299 cells, the mean was 166.4 cells. Mitotic indices of proliferated lymphocytes before treatment were 26.4 – 47.6%, the mean was 35.34%, and after treatment was 48.6 – 88.4 %, the mean was 68.57%, and the difference between before and after treatment was 13-59.8, the mean was 33.24%.
The results of the COVID-19 patients group revealed lower numbers of proliferated PHA-non-treated lymphocytes than in the healthy group (25 – 142; the mean was 75.38 cells). When stimulated with PHA, higher numbers of T cells transferred to lymphoblasts (250-387; the mean was 318 cells). The difference between before and after treatment with PHA was 162-315; the mean was 242.6 cells. As a result, there were higher differences between proliferated T cell numbers before and after treatment in the COVID-19 patients group than in the healthy control group. Consequently, a higher mitotic index at the difference between before and after treatment was found for COVID-19 patients group (32.4% – 63%, the mean was 48.53%) than for healthy control group (13% -59.8%, the mean was 33.24%) as shown in table 2.

parameter	Minimum	Maximum	Mean	Std. Deviation
Age (years)	3.00	70.00	25.76	20.206
WBCs count (total)	3.60 (x1o³)	20.70 (x1o³)	10.36 (x1o³)	3.895
Neutrophiles (%)	29.80	89.80	68.06	17.997
Lymphocytes (%)	4.20	61.00	25.34	16.858
Monocytes (%)	2.60	10.50	5.49	2.084
Esinophiles (%)	0.00	1.60	0.48	0.475
Basophils (%)	0.20	2.40	0.59	0.469
PHA-treated T cells	250.00	387.00	318.04	43.493
Non-treated T cells	25.00	142.00	75.38	30.452
Difference between treated and non-treated T cells	162.00	315.00	242.66	39.479
Mitotic index of treated T cells	50.00	77.40	63.60	8.698
Mitotic index of non-treated T cells	5.00	28.40	15.07	6.090
Mitotic index of difference between treated and non-treated T cella	32.40	63.00	48.53	7.895

Table 2. Descriptive statistics of tested parameters for COVID-19 patients group.

A prominent figure in COVID-19 is the presence of lymphopenia, i.e., a decrease in lymphocyte count, as shown in this study. These cells showed a higher capacity to proliferate in the case of COVID-19 patients than in healthy. The comparison of mitotic indices of proliferated lymphocytes between COVID-19 patients and healthy showed a highly significant increase in T cells stimulated by PHA in COVID-19 patients than in the healthy group, as the difference between indices before and after treatment was too high (t= 5.051, sg (2-tailed) =0.0).
Untreated lymphocytes in the patients' group were significantly lower than that of the healthy group (t= 11.268, sig (2-tailed) = 0.0), but when stimulated with PHA, a significant increase in the number of these cells were proliferated to lymphoblasts as shown in table 3.

	t-test for Equality of Means

Parameter	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
						Lower	Upper
Age	-0.371	41	0.713	-1.807	4.876	-11.655	8.040
WBC	-1.703	41	0.096	-1.855	1.089	-4.055	0.344
Neutrophils	-1.812	41	0.077	-7.534	4.157	-15.931	0.862
Lymphocytes	1.651	41	0.106	6.356	3.850	-1.419	14.132
Monocytes	0.285	41	0.777	0.154	0.544	-0.945	1.255
Eosinophils	4.967	41	0.00	1.314	0.264	0.779	1.848
Basophils	1.624	41	0.112	0.282	0.173	-0.068	0.632
PHA-treated T cells	1.661	41	0.105	24.816	15.018	-5.515	55.147
Untreated T cells	11.268	41	0.000	101.346	8.994	83.182	119.510
Difference between treated and untreated T cells	-5.05	41	0.000	-76.530	15.394	-107.619	-45.441
MI of PHA-treated T cells	1.652	41	0.106	4.963	3.003	-1.103	11.029
MI of untreated T cells	11.268	41	0.000	20.269	1.798	16.636	23.902
MI of the difference between treated and untreated T cells	-5.05	41	0.000	-15.306	3.078	-21.523	-9.088

Table 3. The t-test results of the comparison between the healthy control group and the COVID-19 patients group in the parameters tested.
Notes: MI= mitotic index, PHA= phytohemagglutinin, WBC= white blood cells.

Effect of SARS-COVID-19 on the white blood cells:

The total white blood cell count of the COVID-19 patients' group ranged between 3.6 – 20.7, and the mean was 10.36x10³(cells\ul) compared to 4.4-19.5, the mean was 8.5x10³ (cells\ul) in the healthy group with no significant difference between the two groups.

Neutrophils percentage of the patients group ranged from 29.8% – 89.8%, the mean was 68.06% compared to 45.5% -72.4%, the mean was 60.52% in the healthy control with no significant difference between them.

The lymphocyte percentage of the patients group ranged from 4.2% - 61%; the mean was 25.34% in contrast to 20.7%-43.5%; the mean was 31.7% in the healthy ones.

Despite lymphopenia in the COVID-19 patients' group, the differences between the patients and healthy groups were insignificant (t=1.651, sig (2-tailed) = 0.106).

The monocyte percentage of the patient's group ranged from 2.6% -10.5%; the mean was 5.49%, nearly similar to the healthy control (3.1% - 8.7%, the mean was 5.64%) with no significant difference.

Eosinophils percentage ranged from 0.0 – 1.6 %; the mean was 0.48 % in the COVID-19 patients compared to o.4% – 4.6%; the mean was 1.80 % in the healthy control. The decrease of eosinophils in COVID-19 patients was highly significant compared to the healthy group (t-4.967, sig (2-tailed) = 0.0).

Basophils percentages in the COVID-19 patients ranged from 0.2 – 2.4%, the mean was 0.59 %, while in the healthy group ranged from 0.4 – 3.6 %, the mean was 0.87 % with no significant differences between the two groups.

Discussion

T lymphocytes are the essential arm of defense against viral infections, including SARS-COV-2 and coronavirus, and might mainly act on lymphocytes, especially T lymphocytes (11). Many studies investigated the state of T lymphocytes in COVID-19 patients at different stages of severity with contradictory results. Most of these studies used the flow cytometry technique to test lymphocyte proliferation activity in response to different stimuli, especially coronavirus antigens. In this study, we used the conventional lymphocyte proliferation assay and PHA as mitogenic stimulus since the flow cytometry technique requires large quantities of blood that cannot be obtained from COVID-19 patients in this study and the unavailability of coronavirus antigens used for lymphocyte stimulation.

Lymphocyte count varies with different viral infections and viral types. In this study, lymphopenia is prominent but with no significant difference between patients and healthy groups. Many studies reported a significant decrease in lymphocyte numbers associated with severity progress [12, 13, 14, 15]. In this study, lymphopenia was marked at the first few days of infection, which may be attributed to a direct invasion by the virus or apoptosis induced by interleukins or cytokine storm-induced atrophy of lymphoid organs or reduced proliferation by lactic acidosis as suggested by [12] but not a deficient immunological response to viral infection as suggested by [9] because PHA-stimulated lymphocytes, despite marked lymphopenia, reveal an excellent response to the mitogen. Similar results were found in a study of patients at different stages of the disease in which severe COVID-19 patients at the third week of infection had a higher degree of proliferation, activation, and cytotoxic T-cells than patients at the first week of the disease. [16]

A study by (17) found that CD25+ CD4+ T cell count is negligible. However, he supposed that FURIN expression in these T cells contributes to enhancing viral entry that mediates through either SARS-COV-2 infection of T cells or enhancing virus entry into dendritic cells with which Ag-specific T cells may interact.

[18] Suggested that SARS-COV-2 enters T-lymphocytes by alternative receptors since T-lymphocytes do not express ACE2.

Nineteen reported that CD25+ CD4+ T cells in severe cases are abnormally activated. However, they fail to differentiate into specific T-cell subsets in which activation or differentiation may be stopped prematurely at an early activation stage and contribute to the infection and pathogenesis.

Differential white blood cells in COVID-19 patients

Different studies emphasized that most COVID-19 patients share standard CBC parameters alterations related to the disease progression and severity [20] and patients, especially hospitalized, should undergo daily CBC tests to monitor changes predictive of poor outcomes [12]

Neutrophiles

In many studies, these cells are associated with many viral infections and increase in number in more severe forms associated with cytokine storms9. In this study, there is no significance in the differences between the patients and healthy groups, possibly due to the sampling time or to a mild severity of symptoms.

Monocytes

These cells express ACE2 and can be infected by coronavirus at a deficient virus replication [21, 22]. Decreased number of monocytes associated with severity progression in many studies. In contrast, a high proportion of normal monocytes is associated with earlier recovery [21]. In this study, nearly equal numbers of monocytes were found in the patients and healthy groups, possibly due to a prematurity of the infection.

Eosinophils

Eosinophils play essential roles in allergy and parasitic infections, but their role in coronavirus disease is unknown. Many studies pointed to esinopenia in SARS-COV-2 patients at admission [23] ranged from mild to significant decrease associated with progression of severity [24]. In contrast, in another study, there was an inverse relation of eosinophils with the severity of the disease [25]. The role of eosinophils in the pathophysiology of coronavirus disease is suggested to be related to different factors like cell movement to the site of inflammation, inhibition of mobilization from bone marrow, blockade of eosinophil production, and direct apoptosis [26, 27]. In this study, a significant decrease in eosinophils in COVID-19 patients compared to the healthy at the first few days of the infection suggests a putative role of these cells in the COVID-19 pathophysiology.

Basophils

Like eosinophils, basophils leave the circulation toward the inflammatory sites during allergic infections [28] and, after activation, enhance B cells to secrete immunoglobulins [29]. It is known that IL-4 produced by eosinophils and basophils stimulates T and B lymphocytes for proliferation [30]. In this study, basophils decreased in COVID-19 patients, although non-significantly, and this reduction in number, in addition to eosinopenia, may further explain the decrease in lymphocyte count.

Conclusion

This study concluded that SARS-COV-2 causes a decrease in lymphocytes and eosinophil counts in the circulation during the first week of the infection. Although lymphocyte count decreases in the circulation, SARS–CoV–2–infected lymphocytes are highly stimulated to proliferate when treated with the non-specific mitogen. This study suggests that cellular immunity did not impair, at least at the first week of the infection. Further studies using the lymphocyte proliferation test at the following stages of the disease are required to understand the role of T-lymphocytes and other white blood cells in the pathophysiology of coronavirus infections to establish the proper management and control of COVID-19 infection.

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