TANAFFOS

Late Post-Coronavirus Disease 2019 Inflammatory Syndrome: A Case Experience with Tocilizumab

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Dear Editor

Case 1:

On March 19, 2020, an otherwise healthy 45-year-old male case with no medical or drug history was admitted to Masih Daneshvari Hospital, Tehran, Iran, with the presentation of fever, chills, anorexia, fatigue, cough, shortness of breath, and pleuritic chest pain. Reverse transcription-polymerase chain reaction (RT-PCR) and chest computed tomography (CT) previously performed were negative for coronavirus disease 2019 (COVID-19).

Three weeks earlier, the case was confirmed to have COVID-19 by a positive RT-PCR test and bilateral chest infiltrate and was treated with lopinavir/ritonavir in accordance with the national guidelines. Subsequently, the case was discharged with an acceptable clinical condition and a negative RT-PCR test.

Laboratory parameters and clinical characteristics are reported in tables 1 and 2, respectively. Pulmonary CT angiography revealed positive results for pulmonary embolism. The patient received therapeutic heparin (80 units/kg intravenous bolus, followed by a continuous infusion of 18 units/kg/hour) and was closely monitored for hemodynamic instability.

Over the next 48 hours, the patient's symptoms did not improve, and he had elevated erythrocyte sedimentation rate (ESR), D-dimer, and C-reactive protein (CRP) levels, with no other risk factors for pulmonary embolism, indicating that a COVID-19-related hypercoagulable state was the possible reason for pulmonary vasculature thrombosis. The level of interleukin 6 (IL-6) was observed to be high (Table 1).

Based on clinical and laboratory features, the patient was diagnosed with a delayed postviral COVID-19 cytokine release storm. At this time, tocilizumab was considered the best treatment choice. Therefore, the patient was treated with a single dose of 400-mg tocilizumab (Actemra; Hoffmann-La Roche Limited).

The patient was discharged from the hospital with a stable condition 3 days later (Table 2). He was followed up until June 20, 2020, to be monitored for potential symptom relapse, and there were no episodes of symptom relapse or need for hospital readmission during 3 months.

Table 1. Laboratory findings of two patients infected with COVID-19

Variable	Patient 1	Patient 2
Blood routine		
WBC (× 10⁹ cells/L) (normal range 3.5–9.5)	5	13.9
Lymph (× 10⁹ cells/L) (normal range 1.1–3.2)	1.3	1
Hgb (g/L) (normal range 125.0–175.0)	125.5	170
PLT-Count (× 10⁹ cell/L) (normal range 125.0–350.0)	150	230
Blood biochemistry		
BUN (mmol/L) (normal range 3.1–8.0)	3.5	4
Cr (µmol/L) (normal range 59.0–104.0)	60.4	73.2
AST (U/L) (normal range 0.0–40.0)	32	18
ALT (U/L) (normal range 0.0–41.0)	29	23
Coagulation function		
D-dimer (µg/mL) (normal range 0.0–0.5)	2.8	0.4
Infection-related biomarkers		
CRP (mg/L) (normal range 0.0–1.0)	49	73
ESR (mm/h) (normal range 0.0–20.0)	80.5	100
Inflammatory mediators		
IL-6, pg/mL (normal range 5-15 pg/ml) at baseline	38	30.1
IL-6, pg/mL (normal range 5-15 pg/ml) 48hs after tocilizumab	4	5

WBC: White blood cells; Lymph: Lymphocyte; Hgb: Hemoglobin; PLT-Count: platelet; BUN: Blood urea nitrogen; Cr: Creatinine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6.

Table 2. Clinical characteristics of two patients infected with COVID-19, before and after tocilizumab administration

Variable	Patient 1	Patient 2
Temperature (°C) at baseline	38.5	38.7
Temperature (°C) 24hs after tocilizumab	36.5	36.7
Heart Rate (beats/minute) at baseline	130	120
Heart Rate (beats/minute) 24hs after tocilizumab	75	82
Respiratory Rate (breaths/minute) at baseline	30	24
Respiratory Rate (breaths/minute) 24hs after tocilizumab	19	19
Blood Pressure (mmHg) at baseline	115/90	110/90
Blood Pressure (mmHg) 24hs after tocilizumab	125/95	115/95
O₂ Sat (%) at baseline	85	92
O₂ Sat (%) 24hs after tocilizumab	96	95

Case 2:

On March 29, 2020, a 49-year-old male case was referred to an emergency department with 5 days of fever, dry cough, and dyspnea on exertion. The patient had no underlying diseases or history of medicine usage; however, he was confirmed to have COVID-19 by a positive RT-PCR test one month ago and was treated with an antiviral drug (i.e., favipiravir). Laboratory measurements showed elevated white blood cell, CRP, ESR, and IL-6 levels (Table 1).

The patient was diagnosed with a delayed postviral COVID-19 cytokine release storm. Tocilizumab (Actemra; Hoffmann-La Roche Limited) was infused as a single dose of 400 mg over 2 hours. The patient was discharged from the hospital on the 4th day with oxygen saturation of 95% and an acceptable clinical condition (Table 2). He was followed up until June 20, 2020, to be monitored for possible episodes of symptom relapse and need for hospital readmission. He reported no medical problems.

DISCUSSION

Herein, we reported two cases of late systemic inflammatory responses induced by COVID-19 after several weeks. These responses were characterized by the release of IL-6, which induced a cytokine storm. Certain reports have shown that severe acute respiratory syndrome coronavirus 2 binds to alveolar epithelial cells and activates the innate and adaptive immune systems, resulting in the release of numerous cytokines (1).

In the current cases, we faced a delayed cytokine storm, which occurred several weeks after infection with COVID-19. High serum levels of IL-6 in COVID-19 can occur in later stages (2). The interaction of adaptive and innate immune responses might temporarily decrease the level of virus ribonucleic acid (RNA). However, if the virus is not completely cleared, late mast-cell activation leads to the release of pro-inflammatory cytokines, such as IL-6 (3).

Another study observed the clinical course of the multisystem inflammatory syndrome, which was treated with IL-6 inhibitors (4). Lai et al. reported the patients with COVID-19 whose conditions deteriorated suddenly in the later stages of the disease or in the process of recovery (5). Moreover, in-vitro cell experiments showed that the delayed release of cytokines occurred in respiratory, immune cells in the early stage of COVID-19 (6). Furthermore, a study of patients with administered corticosteroids for the Middle East respiratory syndrome-related coronavirus infection revealed a delay in coronavirus RNA clearance approximately 30 hours later (7).

Other studies described the overproduction of pro-inflammatory cytokines in patients with COVID-19, which induced localized microvascular inflammation. This process leads to an increased risk of vascular hyperpermeability and pro-thrombotic conditions (8, 9). Likewise, the finding of raised D-dimer concentrations as a prognostic feature in severe COVID-19 pneumonia indicated the activation of the coagulation pathways (10, 11). One treatment option might be IL-6 inhibition by tocilizumab (12, 13).

Herein, we have reported the successful treatment of two patients with late-onset hyperactivated immunity pathways several weeks after infection with COVID-19 and achieved rapid control of hyperinflammation by blocking the IL-6 receptor using tocilizumab.

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