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Patients with COVID-19-Associated Hematologic Abnormalities and the Potential Role of the Cytokine Storm: A Case Series Study

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ABSTRACT

We report a case series of nine patients with confirmed coronavirus disease 2019 (COVID-19) in Tehran, Iran. This paper also reports narrative information on the signs and symptoms of the patients and discusses the potential immunologic perspective of the disease, especially with respect to the cytokine storm.

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INTRODUCTION

The world is facing the coronavirus disease 2019 (COVID-19) pandemic with millions of severe infections and fatalities. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causing agent of COVID-19, raised global concerns because of its novelty, communicability, and rapid spread. Hitherto, several studies have described clinical characteristics, radiological abnormalities, and pathological features of patients with COVID-19 [1]. The most frequent site of infection with SARS-CoV-2 appears to be the lungs as pneumonia, and it manifests primarily as fever, cough, dyspnea, and lung infiltrates on chest imaging modalities. However, other signs and symptoms, including headache, myalgia, nausea, diarrhea, and loss of smell or taste, have also been prevalently reported [1]. Although we have learned a lot about COVID-19 and its pathogenesis, the knowledge around it is still evolving. In this paper, 9 cases of confirmed COVID-19 that includes narrative information of signs and symptoms on admission and during hospitalization for each case are discussed while the unique aspect of each patient is presented.

MATERIALS and METHODS

Ethical Statement

Publication of this case series was approved by the institutional review board of Tehran University of Medical Sciences, and written informed consent was obtained from each patient or in the case of deceased patients from next of kin.

Study Plan

In this case series, we share our experience of 9 cases diagnosed with COVID-19 based on clinical manifestations. The diagnosis was confirmed by chest CT-scan and RT-PCR analysis of the nasopharyngeal swab samples within 48 h of their hospital admission. The treatment was determined based on the Iranian interim guidelines for the management of COVID-19 and the compassionate use of other medications based on the clinical settings [2]. Criteria for discharge with full recovery were also adopted from the Iranian interim guidelines for the management of COVID-19 as remaining afebrile for at least 48 h with PaO_2 > 93% on room air, and remarkable improvement in the respiratory condition and chest imaging studies.

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Case Presentations

Case 1: A 37-year-old male was referred to the Emergency Department (ED) with illness symptoms in the past 10 days including fever, chill, myalgia, nonproductive cough, and chest discomfort. Due to a recent illness, he had received corticosteroids and penicillin in an outpatient clinic a few days ago, and had no other medical history. On arrival to ED, he was febrile, with oxygen saturation (O_2 Sat.) of 98% on room air. On physical examinations, bilateral crackles in inferior lobes of lungs were auscultated. The chest CT scan revealed multifocal bilateral patchy ground-glass opacities with crazy paving dominantly distributed in the periphery of the lungs. An upper respiratory tract swab was taken from the patient, and the result of RT-PCR was positive for SARS-CoV-2 within 48 h. His laboratory data revealed a leukocyte count of 4100/ml with 81% neutrophil, a platelet count of 132000/ml, and a normal level of creatinine. Besides, he had a high level of urea (36 mmol/L) and the C-reactive protein (CRP) was also elevated (93 mg/L). He was treated with 400/100mg lopinavir/ritonavir (Kaletra), 75 mg Oseltamivir twice a day, and a single dose of 400 mg Hydroxychloroquine for 5 days, and he was discharged uneventfully.

Case 2: A 55-year-old male was referred to the ED due to the high suspicion of COVID-19. He had productive coughs, dyspnea, nausea, and myalgia, as well as recent travel history, and exposure to COVID-19 patients. Otherwise, his past medical history was uneventful. At the hospital admission, he was febrile, and bilateral peripheral and multifocal patchy ground-glass opacities, which were predominant in the lower zone of lungs, were evident on chest CT-scan. Eventually, RT-PCR on the nasopharyngeal swab for SARS-CoV-2 was positive. All necessary tests were taken and initial CBC showed a low level of WBC (3800/ml) with 80% neutrophil. Other laboratory data revealed a low level of platelets (94000/ml), a high level of urea (48 mmol/L) with a normal level of creatinine, and also a high level of CRP (96 mg/L). The treatment was started with 100/400 mg Kaletra and 75 mg Oseltamivir twice a day, a single dose of 400 mg Hydroxychloroquine, daily injection of 750 mg levofloxacin, and at last 1 g vancomycin two times a day. On the 4th day of hospitalization, while he complained of difficulty in breathing and had mild respiratory distress, his respiratory rate was 44/min, O_2 Sat. was 84% without mask and it rose to 96% with mask. He was transferred to ICU given the patient's rising oxygen requirement, and was discharged after 7 days of aforementioned treatment.

Case 3: A 46-year-old female was referred to the ED with a history of fever, chills, nonproductive cough, abdominal pain, and non-bloody diarrhea for the last 7 days. Her past medical history was only notable for hypertension. An initial chest CT-scan showed a few focal points of patchy ground-glass opacities in the periphery of both lungs. Her upper respiratory tract swab for SARS-CoV-2 RT-PCR returned positive. Initial laboratory testing was notable for a drop in WBC count (2700/ml) with increased neutrophil percentage, and a low platelet count of 127000/ml. CRP was significantly elevated up to 132 mg/L. The triple drug therapy regimen was started with a single dose of 400mg Hydroxychloroquine, and both 75 mg Oseltamivir, and 100/400 mg Kaletra twice a day for 5 days. After 24 h of admission, she was discharged to continue her treatment at home.

Case 4: A 61-year-old healthcare worker was admitted to the hospital with dyspnea and myalgia. He has an occupational exposure to a suspected COVID-19 patient. His O_2 Sat. was 85% on room air, which was increased to 93% with oxygen supply. A chest CT scan was performed, which demonstrated bilateral multifocal patchy ground-glass opacity (GGO). Subsequently, upper respiratory tract RT-PCR for SARS-CoV-2 was positive. Also, the primary lab result was only notable for an increase in neutrophil percentage and anemia presented as low hemoglobin level. He was treated with 100/400 mg Kaletra, and 1200 mg Ribavirin twice a day, and a single dose of 400 mg Hydroxychloroquine. Due to the persistent hypoxemia, he was placed on BiPAP ventilation, and remained stable to date.

Case 5: A 55-year-old female with a past medical history of diabetes mellitus came to ED with complaints of weakness while her O_2 Sat. on room air was 89%. The initial chest CT scan revealed no abnormal findings; however, the patient's upper respiratory tract swab for SARS-CoV-2 RT-PCR was positive. Lymphopenia (10%) with normal leukocyte count and high level of CRP were the only abnormal findings on initial workup. She was treated with a proper dose of Insulin, 75 mg Oseltamivir twice a day, and 400mg Hydroxychloroquine for 5 days and after which she was successfully discharged home in good condition.

Case 6: A 54-year-old female patient with no known comorbidity was admitted to the hospital with complaints of dry coughs, fever, and myalgia. On admission, she had fever and tachycardia. She was diagnosed with COVID-19 pneumonia with demonstrated multifocal patchy ground-glass infiltration in the inferior lobe of the right lung on her chest CT-scan. Besides, laboratory tests showed lymphopenia (12%) with normal leukocyte count. The treatment started with 400 mg Hydroxychloroquine. After 24 h, she developed vertigo, sweating, and confusion while her blood glucose level was 46 mg/dL. Based on her history and since Hydroxychloroquine may lead to increased insulin level and subsequent hypoglycemia, one vial of 50% Dextrose was administered, and the Hydroxychloroquine dose was reduced to half. The hypoglycemia did not repeat, and she was discharged 5 days later, uneventfully.

Case 7: A 55-year-old male with no remarkable medical history except for cervical mass diagnosed with papillary thyroid carcinoma was admitted with a complaint of shortness of breath. A chest CT scan on admission revealed ground-glass lesions in both lungs, particularly in the lower lobe of the left lung, suggesting the COVID-19 infection. Subsequently, a PCR of nasopharyngeal swab confirmed SARS-CoV-2 infection. Laboratory tests revealed lymphopenia and a high level of CRP and abnormal INR (4.2). Due to the massive cervical mass, and its obstructive effect on the esophagus, a nasogastric tube could not be placed to initiate the treatment. Besides, due to the high INR, performing jejunostomy was impossible. The oxygen saturation was 87% at the admission; however, it increased to 97% after intubation and remained around 95% after 25 days of admission without any other treatment.

Case 8: A 44-year-old female with a history of myasthenia gravis and consequent thymectomy presented to the ED with persistent non-productive cough, dyspnea, nausea, and myalgia for 7 days. A chest CT scan was performed and showed bilateral patchy high-density shadow in both lungs and consolidation with air bronchogram, especially in left parenchyma. An upper respiratory tract swab was obtained from the patient which turned to be positive for SARS-CoV-2. The patient's myasthenia gravis had been diagnosed with swallowing difficulty, blurred vision, ptosis, and dyspnea last year, following thymectomy and the pathology of type B2 SCI erosing invasive thymoma. She had been treated with

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radiotherapy of the bed of thymus and rituximab following surgery, and then mestinon and prednisolone. Daily prednisolone with a dose of 12.5 mg continued to date. After admission, the patient received supportive care and treatment including supplemental oxygen through a face mask, and a combination of medications consisting of Atazanavir daily, Sofosbuvir/Ledipasvir 400/90 mg daily, Oseltamivir 75 mg twice a day, and a single dose of Hydroxychloroquine 400 mg following with 200 mg every 12 h. Due to high suspicion of bacterial superinfection, intravenous Ceftriaxone 1 g twice daily, and Intravenous clindamycin 900 mg 3 times a day, were administered.

On the second day of hospitalization, she developed weakness and dyspnea, and her O_2 Sat. dropped to 85% on room air. The dose of Hydroxychloroquine was increased to 400 mg every 12 h, and vitamin B1 (300 mg daily) was prescribed to improve the patient's condition. On the fourth day of hospitalization, the O_2 Sat. increased to 92% breathing room air but there was a sudden onset of nausea. Diphenhydramine syrup (10 ml every 8 h) was started. On the fifth day of hospitalization, the patient began to develop respiratory distress, and O_2 Sat. decreased to 85% breathing room air. Troponin was checked, and a chest x-ray was done that was not in favor of increased involvement of the lungs. A single dose of intravenous Methylprednisolone 250 mg and intravenous vitamin C (1.5 g every 6 h) was prescribed.

On the day 6 of hospitalization, the patient's respiratory status was relatively improved, and O_2 Sat. was 90% on room air. As the course of Oseltamivir, Ceftriaxone and Clindamycin were completed, they were all discontinued, and Azithromycin 500 mg started. Because of the increased risk of QT prolongation with the regimen, ECG was monitored daily. During the second week of hospitalization, the patient's respiratory condition improved dramatically with O_2 Sat. increased to 95% breathing air room, and her symptoms resolved. She was ultimately discharged from the hospital with Hydroxychloroquine (200 mg twice a day) to complete a 10-day course, and Azithromycin 500 mg daily to complete a five-day course.

Case 9: A 43-year-old female presented to the ED with progressive weakness, myalgia, and fever. She complained from tingling sensations in her fingers, 3 days before hospitalization, resulting difficulty in buttoning her shirt. After 12 h, her arms felt weak, and she could not comb her hair. On the next day, she developed foot dysaesthesia and ascending weakness of the lower limb which leads to difficulty in mobilizing. Incidentally, she also reported a history of mild cough, fever, and myalgia, 1 week before the onset of her neurologic symptoms. She was not on regular medications, but had taken over the counter medications to relieve her chronic intermittent diarrhea.

On initial presentation to the ED, she was afebrile with oxygen saturation of 93% on room air. Limb examination revealed reduced tone with symmetrical weakness of 3/5 in proximal upper limbs and 2/5 in distal upper limbs. Reduced tones with symmetrical weakness of 2/5 in proximal and distal lower limbs were also noted. Her muscle reflexes were diminished at triceps, brachioradialis, and knee bilaterally but were normal at bicep bilateral. Also, her achilles reflexes were mute on both sides. Her initial laboratory workup showed a white cell count of 3700 with 46% neutrophil and 41% lymphocyte, and a slightly decreased platelet level (144000). She had a mildly elevated CRP and ESR. In addition, her serum electrolytes levels, renal function, and liver function were normal. The overall impression was of a progressive flaccid symmetrical sensory and motor neuropathy.

Given the ongoing outbreak of COVID-19, history of symptoms of fever and cough, and chest CT scan findings, SARS-CoV-2 infection was suspected, and the treatment was started based on the guideline for COVID-19. While still undergoing initial workup, 1 day after hospitalization, her lower limb power reduced proximally to the point that she could not get out of her bed and was not able to stand unaided. Moreover, she developed symptoms of dysautonomia as manifested by fluctuating blood pressure and heart rate.

Her cerebrospinal fluid (CSF) showed a protein level of 57.7 g/L, a sugar level of 54 mg/dL, and LDH level of 26 with no cell. Based on her clinical history and neurologic examination, CSF analysis findings, history of recent infection, negative brain MRI results, and axonal motor acute polyneuropathy on EMG/nerve conduction studies, a diagnosis of Guillain-Barré syndrome was made. The patient was started on 15 g of intravenous immune globulin (IVIG) therapy twice a day for a planned 5-day course. The patient's neurologic symptoms began to improve within the first week of treatment, and she was discharged after 14 days.

Table 1 shows the demographic, clinical, imaging, and laboratory characteristics of the patients with COVID-19.

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Table 1. Demographic**,** clinical, imaging, and laboratory findings of the patients with COVID-19 in the hospitals, Tehran, 2020.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Demographics									
Gender	Male	Male	Female	Male	Female	Female	Male	Female	Female
Age (yrs.)	37	55	46	61	55	54	55	44	43
Comorbidities									
Hypertension	No	No	Yes	No	No	No	No	No	No
Diabetes mellitus	No	No	No	No	Yes	No	No	No	No
Papillary thyroid carcinoma	No	No	No	No	No	No	Yes	No	No
Myasthenia gravis	No	No	No	No	No	No	No	Yes	No
Symptoms and signs									
Fever	Yes	Yes	Yes	No	No	Yes	No	No	Yes
Chills	Yes	No	Yes	No	No	No	No	No	No
Myalgia	Yes	Yes	No	Yes	No	No	No	Yes	Yes
Cough	Yes	Yes	Yes	No	No	No	No	Yes	Yes
Chest pain	Yes	No	No	No	No	No	No	No	No
Nausea	No	Yes	No	No	No	No	No	Yes	No
Dyspnea	No	Yes	No	Yes	No	No	Yes	Yes	No
Abdominal pain	No	No	Yes	No	No	No	No	No	No
Diarrhea	No	No	Yes	No	No	No	No	No	No
Tachycardia	No	No	No	No	No	Yes	No	No	No
Weakness	No	No	No	No	Yes	No	No	Yes	Yes
Dysaesthesia	No	No	No	No	No	No	No	No	Yes
Lower limb weakness	No	No	No	No	No	No	No	No	Yes
Chest CT findings									
Bilateral peripheral and multifocal patchy ground-glass opacities	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No

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Chest CT findings									
Bilateral peripheral and multifocal patchy ground-glass opacities	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
Laboratory findings									
O_2 Sat	98%	84% and 96% without and with mask	-	85%without and 93% with oxygen supply	89%	-	87% on admission	85%	93%
RT-PCR on the nasopharyngeal swab	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Leukocyte count (cells/ml)	4100 with 81% neutrophil	3800 with 80% neutrophil	2700 with increased neutrophil percentage	Increase in neutrophil percentage	Lymphopenia (10%) with normal leukocyte count	Lymphopenia (12%) with normal leukocyte count	Lymphopenia	-	3700 with 41% lymphocyte
Platelet count (cells/ml)	132000	94000	127000	-	-	-	-	-	144,000
Urea (mmol/L)	36	48	-	-	High level	-	-	-	-
Creatinine	Normal	Normal	-	-	-	-	-	-	-
C-reactive protein (mg/L)	93	96	132	-	-	-	High	-	Mildly elevated
INR	-	-	-	-	-	-	4.2	-	-
Drugs									
Used before	Corticosteroid and penicillin	-	Anti-hypertensive	-	-	-	-	Prednisolone	Over the counter medications
Prescribed	Lopinavir, ritonavi, oseltamivir and hydroxy chloroquine	Kaletra, oseltamivir, hydroxy chloroquine, levofloxacin and vancomycin	Hydroxy chloroquine, oseltamivir and kaletra	Kaletra, ribavirin and hydroxy chloroquine	Insulin, oseltamivir and hydroxy chloroquine	Hydroxyl chloroquine and dextrose	-	Atazanavir, sofosbuvir, ledipasvir, oseltamivir, hydroxy chloroquine, ceftriaxone, clindamycin, methylprednisolone and azithromycin	Immune globulin

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DISCUSSION

This multicenter case series describes nine COVID-19 patients. Although these patients represent a heterogeneous group of presentations, there are several features common among them. Hematologic abnormalities including lymphopenia with greater neutrophil to lymphocyte ratio and less commonly low platelets are among the features shared between the cases. Eight of the patients had low white blood cell counts and lymphopenia. On the other hand, roughly half of the cases showed thrombocytopenia. Emerging evidence shows that the immune responses are closely associated with the incidence of such hematologic abnormalities. Indeed, the immune system can serve as potential biomarkers for the disease progression and prognosis as well as the therapeutic targets [3].

Lymphopenia appears to be one of the major hematological abnormalities associated with SARS-CoV-2 infection and related mortality. There have been multiple mechanisms suggested that lead to lymphocyte depletion and exhaustion, such as lymphocyte sequestration in the tissues, virus-mediated lymphatic organ suppression, and induction of lymphocytes apoptosis by the virus and cytokines. Due to impaired lymphocyte function, activation and recruitment of neutrophils up-regulated in patients can lead to disproportionately high neutrophil to lymphocyte ratio [4]. Although immunologic mechanisms have been suggested for thrombocytopenia associated with COVID-19, it is worth noting that lung impairment along with the reduction of platelet production may also play a role [5, 6].

Inflammatory cytokine production is overwhelmingly increased in severe COVID-19 over a short period, which is commonly referred to as a cytokine storm. This phenomenon can result in organ damage, acute respiratory distress syndrome (ARDS), respiratory failure, and potentially death [7]. The effects of some serum levels of these cytokines on lymphocytes levels in COVID-19 patients have been explored. For instance, it has been shown that there is a negative correlation between TNF-α levels and lymphocyte counts in such patients. It is believed that TNF-α directly causes lymphocyte apoptosis and subsequently lymphopenia. IL-10 is another anti-inflammatory cytokine that has been shown to negatively regulate T cell survival or proliferation [8, 9]. Another effect of cytokine release in COVID-19 is the destruction of hematopoietic progenitor cells and consequent decline in platelet production which contribute to the thrombocytopenia [10].

In conclusion, in this case series study of 9 patients with COVID-19-associated hematologic abnormalities, although the cytokines level of the patients were not evaluated, we suggest an underlying role of the cytokine storm to cause such abnormalities. Hence, it would be important to not only explore the role of blood count abnormalities in the choice of therapeutics, but also to use such cytokine biomarkers to follow up on the patients and access their response to the treatments.

CONFLICT OF INTEREST

The authors declare they have no conflict of interests.

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