Hemophagocytic lymphohistocytosis in a COVID-19 patient in the acute phase: case report

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Summary The outbreak of coronavirus disease 2019 (COVID-19) has put health systems worldwide under great pressure on numerous levels. COVID-19 is a heterogeneous situation where some people experience mild symptoms for which no serious intervention is needed, while others may experience serious situations ranging from acute respiratory distress syndrome (ARDS) or even respiratory failure and end organ damage. Serious COVID-19 cases may be complicated with a cytokine storm caused by hemophagocytic lymphohistocytosis, which is a life-threatening situation. Efforts should be directed to reveal accompanying diseases that may trigger the cytokine storm. Early diagnosis leads to a better understanding of how to deal with this emergency status; however, even with early intervention, outcomes are still very poor.

Keywords Covid-19 · Hemophagocytic · Lymphohistocytosis · Acute phase

Introduction

In November 2019, the world witnessed the emergence of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) named later as coronavirus disease 2019 (COVID-19) in Wuhan, China. The virus started to disseminate in Europe and then the United States causing a collapse of both economic and health care sectors. Some patients present with mild symptoms that resolve over time, while others

present with more serious symptoms, which may be complicated with respiratory distress syndrome and multiorgan failure. The latter group necessitates serious medical efforts and the majority of patients need mechanical ventilation [1]. Hemophagocytic lymphohistocytosis syndrome (HLH) can occur in any patient with viral infection and COVID-19 is not an exception. It is characterized by high production of cytokines leading to phagocytosis of white blood cells, red cells, and platelets and it can transform into a septic-like status leading to end organ damage and death. Several reports have documented this syndrome in COVID-19 patients [2]. Hereby, we report the case of a patient in the acute phase of the disease on mechanical ventilation complicated with HLH syndrome.

Case presentation

A 53-year-old patient, admitted to the emergency unit at the Italian hospital in Damascus, Syria on 2 August 2020, presented with dyspnea, tachypnea, cough, and lethargy. On medical exam, he was complaining from shortness of breath, he was pale and confused. Disseminated bilateral crackles on pulmonary auscultation, temperature 38.2°C, blood pressure 100/75 mmHg, heart rate 118 bpm, respiratory rate 28 rpm, O₂ saturation 82%. No hepatosplenomegaly, neither lymphadenopathy. He was offered a nasal mask with an oxygen flow rate of 8 L/min, which improved O₂ saturation to 95%. A nasal and oropharyngeal swab was taken in order to perform a viral panel including COVID-19. A complete blood test panel was taken and included white blood count and differential, platelets, urea, creatinine, electrolytes, liver functions, bilirubin, HCV, HbsAg, INR, LDH, ferritin and glucose. A computed tomography (CT) scan of chest, abdomen and pelvis had also been

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Table 1 Changes in blood tests over the 12 day stay in the intensive care unit

Day	1	3	5	6	7	8	9	10	11	12
Hemoglobin, g/dL	13.4	13.1	9.8	8.1	7.1	6.6	6.2	7.6	6.3	5.8
Leukocytes, 10 ⁹ /L	9.85	11.2	11.8	22.0	28.4	24.1	21.9	18.5	11.3	8.0
Lymphocytes, 10 ⁹ /L	1300	1030	700	480	310	200	110	50	0	0
Platelets, 10 ⁹ /L	240	224	180	360	410	388	122	88	51	22
Urea, mg/dL	55	65	61	67	78	88	110	128	160	144
Creatinine, mg/dL	1.3	1.2	1.5	1.3	1.7	2.1	2.2	1.9	1.8	2.0
C-reactive protein (CRP), mg/dL	177	170	140	133	210	198	167	198	210	199
Lactate dehydrogenase (LDH), U/L	177	228	288	359	910	1360	2030	1950	1810	2000
Ferritin, ng/mL	188	NA	NA	NA	NA	650	889	2130	NA	NA
Alanine aminotransferase (ALT), U/L	23	NA	35	33	45	55	89	110	188	NA
Aspartate transaminase (AST), U/L	17	NA	33	46	77	90	112	177	210	NA
International normalized ratio (INR)	1.6	NA	NA	NA	1.9	NA	2.3	NA	4.7	6.2
Fibrinogen, g/L	NA	313	NA	NA	NA	1.77	NA	NA	1.93	NA
Triglycerides mmol/L	1.7	NA	2.1	NA	NA	3.2	NA	NA	3.3	NA
Hepatitis C virus (HCV) and hepatitis B surface antigen (HbsAg)	Negative	–	–	–	–	–	–	–	–	–

LDH lactate dehydrogenase, CRP C-reactive protein, INR international normalized ratio, ALT alanine aminotransferase, AST aspartate transaminase, HCV hepatitis C virus, HbsAg hepatitis B surface antigen

ordered. While awaiting the results, the patient was admitted to the intensive care unit due to a sudden drop in both blood pressure and saturated O₂. After a central venous catheter was placed in the left internal jugular vein, the patient was put on mechanical ventilation through endotracheal intubation and sedated with lidocaine and rocuronium. A nasogastric tube and a urinary catheter were also inserted. An empirical treatment started including azithromycin and ceftazidime. An additive sedation with fentanyl and a pressure support with norepinephrine were offered. The CT scan revealed disseminated ground-glass pattern in both lungs with fibroblastic changes. The reverse transcription-polymerase chain reaction (RT-PCR) for COVID-19 result was positive. The pa-

tient was hemodynamically stable during the first 6 days of the 12 day stay in the intensive care unit; however, the blood tests were changing daily. The most important changes were the following: anemia, lymphopenia, thrombocytopenia, uricemia and an increase in both ferritin and LDH levels. Table 1 demonstrates the changes in blood tests over the 12 days. As we notice, hemoglobin and lymphocyte count started to deteriorate beginning from day 5, which necessitated a bone marrow aspiration to rule out a hemophagocytic lymphohistocytosis (HLH).

A daily blood smear revealed alterations in leukocytes especially lymphocytes performed along with a bone marrow aspiration on day 6 after the exacerbation of both anemia and lymphopenia. Peripheral blood smears revealed multilobulated neutrophils, some of them demonstrated toxic granules, while lymphocytes started to decrease in number over the last 6 days of follow-up. Lymphocytes showed expanded cytoplasm with vacuoles indicating signs of apoptosis as illustrated in Fig. 2. On the other hand, the bone marrow aspiration demonstrated a very active populated marrow with activation of both the erythroid and the myeloid series with left shift. The main aspect of bone marrow was macrophage activation with phagocytosis of both red cells and late erythroblasts as demonstrated in Fig. 1. The former findings were associated with the worsening of the patient's situation (decrease in O₂ saturation to reach 85–90%, renal failure, hepatic failure and refractory fever). Meropenem was replaced with ceftazidime, and voriconazole was also added due to the appearance of disseminated infiltrations on both lung fields. Dexamethasone was added at 8 mg bid. Unfortunately, we lost the patient on day 12 after 2 consecutive days of anuria and saturation drop to 70–80%.

Table 2 Criteria used to diagnose HLH using H scoring. And the score got by our patient

Parameter	H score	Patient's score
Fever	0 (< 38.4), 33 (38.4–39.4), or 49 (> 39.4)	33
Splenomegaly/hepatomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)	0
Cytopenia	0 (one lineage), 24 (two lineages), or 34 (three lineages) ^c	24
Ferritin (ng/ml)	0 (< 2000), 35 (2000–6000), or 50 (> 6000)	0
Triglycerides (mmol/L)	0 (< 1.5), 44 (1.5–4), or 64 (> 4)	44
Fibrinogen (g/L)	0 (> 2.5) or 30 (≤ 2.5)	30
Hemophagocytosis in bone marrow	0 (no) or 35 (yes)	35
Aspartate aminotransferase (IU/L)	0 (< 30) or 19 (≥ 30)	19
Underlying immunosuppression	0 (no) or 18 (yes)	0
Total sum		185

Fig. 1 Bone marrow aspiration on day 6 shows phagocytosis. Phagocytosis of red blood cells (*green arrow*) and phagocytosis of late erythroblast (*red arrow*)

We have also used the H score for diagnostic purpose with a cut-off value of 169 as determined by Fardet et al. [14]. Table 2 illustrates factors implicated in H score and the criteria met by our patient's factors with the total sum. As observed from Table 1, the sum was 185 which exceeds the cut-off (169) designated by Fardet et al. and the diagnosis of HLH based on our procedures is compatible with that used by H score.

Discussion

Hemophagocytic lymphohistocytosis (HLH) is a situation of hyperactivation of the immune system in response to viral infection or presence of tumor cells. It is a cell-mediated immunity activation of cytotoxic T-cell (CD8) and natural killer cells (NK) leading to uncontrolled immune response mediated by cells, cytokines and consequently major tissue and organ damage [3]. HLH was reported in several viral infection such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus, herpes simplex virus (HSV), varicella-zoster virus and H1N1. It was also reported in cases of COVID-19 [4]. The continuous activation of NK surface toll-like receptors (TLR) by infection [5]. HLH can lead to the cytokine storm characterized by high production of several cytokines, most importantly, $\text{INF-}\gamma$, tumor necrosis factor ($\text{TNF-}\alpha$) and several kinds of interleukins such as IL-2, IL-6, IL-10 and IL-12 causing tissue damage and end organ failure [6]. HLH and COVID-19 infection share some similar features such as fever, cytopenia, lymphopenia, dyspnea, acute respiratory distress syndrome (ARDS) and hepatosplenomegaly, which is more frequently documented in HLH [7]. Laboratory findings in HLH are mainly cytopenia with thrombocytopenia encountered in 60–80% of cases and elevation in both LDH and D-dimer. Ferritin and soluble IL-2 (CD25) elevation are among the main manifestations of HLH [8, 9]. Nonsurvivor COVID-19 patients demonstrate high levels of LDH, ferritin, IL-6, and prolongation in prothrombin (PT) and activated partial thromboplastin (PTT) [10]. Table 1 shows that there is a direct proportion between cytopenia (especially lymphopenia) and aggressive course of disease and HLH. Peripheral blood smears

Fig. 2 Characteristics of blood cells in peripheral blood smear. **a** Cleaved activated lymphocyte (*orange arrow*) **b** vacuoles in nucleus and cytoplasm reflecting the ongoing apoptosis in lymphocyte (*black arrow*), **c** fetus-like lobulation of neutrophils and **d** disappearance of lymphocytes

shows few number of lymphocytes where apoptotic manifestations were clear, e.g., elongations and protrusions of cytoplasm and vacuoles formation in both cytoplasm and nucleus. To date, there is no curative treatment for COVID-19 nor accompanying HLH [11]. HLH treatment should be directed towards the underlying cause and inhibition of the cytokine storm from the very beginning [12] which can be achieved by using dexamethasone and which is considered the drug of choice. In a comprehensive review on treatment of cytokine storm, Fajgenbaum et al. reported some medications to deal with cytokine storm such as interferon γ which decreases neutrophil recruitment to the inflammatory site and corticosteroids which play the role of immune modulator; however, corticosteroids should be used at the right time. Other important and promising agents are anti-TNF- α , interferon $\alpha\beta$, sphingosine-1-phosphate receptor agonist, IL-1 antagonist and stem cell therapy [15]. Associated infections can also be ameliorated by the use of intravenous immunoglobulins (IVIG). High cytokine burden is also decreased to some extent by plasma apheresis or exchange transfusion [13]. In 2014, the Food and Drug Administration (FDA) approved anti-IL-6 (tocilizumab) to control cytokine flash syndrome after treatment with chimeric antigen receptor T-cell (CAR T-cell) [11]. In our report, wide spectrum antibiotics, antifungal, dexamethasone and IVIG were not able to control the HLH which can be attributed either to the aggressiveness of disease course or to the late use of the former medications on day 6. The issue of HLH in the context of COVID-19 should be raised and physicians should deal seriously with every case needing hospitalization, where a complete blood test panel should be performed including CBC, urea, creatinine, LDH, fibrinogen, INR, PT, PTT, ferritin, triglycerides, CRP and cytokine panel whenever possible. We stress early treatment of such cases; however, even with good caution, results are still very poor.

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Declarations

Conflict of interest M. Salamoon and M. Kenj declare that they have no competing interests.

Ethical standards For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case. For images or other information within the manuscript which identify patients, consent was obtained from them and/or their legal guardians.

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