JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

A case of Hemophagocytic lymphohistiocytosis induced by COVID-19, and review of all cases reported in the literature

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Abstract

Novel coronavirus infections 2019 (COVID-19) associated hyperinflammatory syndromes are well-defined clinical conditions and have a potential risk for severe infection. Hemophagocytic lymphohistiocytosis (HLH), a rare type of acute progressive hyperinflammatory syndrome, has been reported in a limited number of COVID-19 cases. In this article, we aimed to present a patient with HLH secondary to COVID-19 diagnosed by bone marrow biopsy, and to summarize and review HLH cases associated with COVID-19 in the literature.

A 47-year-old male patient presented with complaints of fever, cough, abdominal discomfort, and nausea-vomiting. He had recovered from COVID-19 a month ago and was readmitted to the hospital due to the re-appearance of clinical symptoms after a two-week interval. The patient was diagnosed with HLH secondary to COVID-19 on sixth day of admission and fully recovered with systemic pulse steroid, intravenous immunoglobulin, and plasma exchange therapy. Analysis of literature searches revealed that 22 cases were definitely diagnosed with COVID-19-associated HLH, 16 of them were male. They had been treated with different anti-cytokine drugs, of which nine had died. The increasing number of HLH cases, which have high mortality rates, shows the importance of hyperinflammatory syndromes in COVID-19 patients. Some patients may experience hemophagocytosis in the late period of COVID-19, even while in recovery. Increased awareness and early treatment for HLH triggered by COVID-19 can be a life-saving effort for reducing mortality in severe COVID-19 cases.

Key words: COVID-19; SARS-CoV-2; hemophagocytic lymphohistiocytosis; HLH.

J Infect Dev Ctries 2021; 15(11):1607-1614. doi:10.3855/jidc.14829

(Received 02 February 2021 – Accepted 03 April 2021)

Introduction

Hemophagocytic lymphohistiocytosis (HLH), synonymously hemophagocytic syndrome, is a fatal hyperinflammatory syndrome caused by an uncontrollable proliferation of activated lymphocytes and macrophages and thus increased secretion of inflammatory cytokines [1]. It has two forms, primary and secondary HLH. Primary HLH occurs generally due to genetic disorders inherited with autosomal recessively [2]. Secondary HLH occurs reactively to underlying disease including infections, malignity, and autoimmune/autoinflammatory diseases [3]. Viral infections, especially Epstein-Barr virus (EBV) and cytomegalovirus (CMV), and other herpes viruses are well-known triggering factors of HLH. Novel coronavirus disease (COVID-19) has a potential for HLH as it has a wide clinical spectrum from mild disease to severe illness accompanying cytokine storm [3,4]. From the beginning of pandemic, similarities between severe COVID-19 and cytokine storm syndrome have drawn attention [5]. However, HLH, a marginal and potentially fatal form of cytokine storm syndrome, was detected in limited number of COVID-19 patients [6]. Here, we present a case of HLH secondary to COVID-19, in which we demonstrated hemphagocytosis in the bone marrow. In addition, we reviewed and summarized the clinical characteristics and outcomes of all the definitely diagnosed HLH cases induced by COVID-19.

Case Report

A 47-year-old male patient with no known disease before was admitted to the infectious disease's clinic with complaints of fever, cough, abdominal discomfort, nausea-vomiting, myalgia, and loss of appetite and weight (7 kg). He had been diagnosed with COVID-19 a month before, and his fever and other symptoms had resolved within 10 days with treatment. After a two-

week symptom-free period, his complaints had reappeared about a week before and became more severe. The patient was clinically stable at the time of admission, and his blood tests (complete blood count, liver and renal function tests, coagulation tests and inflammation markers) were almost within normal limits except for hyperbilirubinemia (1.5 mg/dL), however, within three days, an unanticipated serious deterioration in the clinical condition and laboratory parameters was observed (Table 1). His fever continued to increase and reached 42 °C, and redness and painful swelling on the neck, and jaundice in sclera and skin appeared. On the fifth day of admission, neurological symptoms including somnolence, disorientation and meaningless speech appeared. In physical examination, cervical lymphadenopathy, liver and spleen enlargement and flapping tremor were observed. Multiple lymphadenopathies in cervical, axillar and femoral sites were detected in superficial ultrasonography. Liver and spleen were at the upper limit in abdominal ultrasonography performed on the first day of hospitalization. Three days later, massive hepatomegaly (22 cm) and splenomegaly (18 cm) were detected in abdominal computed tomography. Thrombocytopenia, anemia, hyperbilirubinemia (dominated direct bilirubin), elevation of aminotransferase, abnormal coagulation tests and hyperferritinemia developed in a few days. No microorganism was detected in culture workup. No causative microorganism was detected in three sets of blood cultures. Serological tests specific for Brucella species (standard tube agglutination test and Coombs tests), Salmonella species (Gruber-Widal test), and *Treponema pallidum* enzyme immunoassay (TP-EIA) were detected negative. Serological tests for viral infections including EBV VCA immunoglobulin M (IgM), CMV IgM, Rubella IgM, anti-HAV IgM, HBsAg, anti-HBs, anti-HCV and anti-HIV tests and multiplex-polymerase chain reaction (PCR) based respiratory viral panels (influenza A and B, respiratory syncytial viruses, parainfluenza virus, adenovirus, rhinovirus and enterovirus) were also negative. Parasitic infection was excluded with negative Toxoplasma IgG, Leishmania dipstick test and Fasciola hepatica IgG. Rheumatological markers including antinuclear antibody (ANA), immunofluorescent tests for anti-neutrophile cytoplasmic antibodies (ANCA) panel and extractable nuclear antigen (ENA) panel were

Figure 1. Findings of hemophagocytosis (host blood cells engulfment by macrophage) in bone marrow examination (May Grunwald-Giemsa Stain).

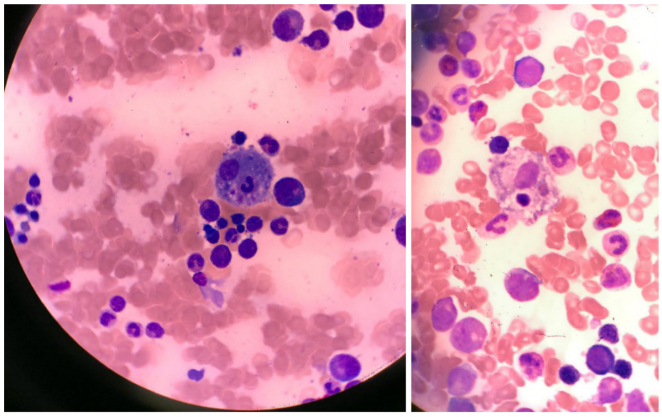


Table 1. Consecutive laboratory parameters according to the days of hospitalization of the patient.

Parameter	Day 1	Day 3	Day 5	Day 7
WBC, 10^9/L	6.360	14.620	21.150	8.650
Hemoglobin, g/dL	12.6	12.1	11.2	9.8
Platelet, 10^9/L	98	74	59	61
GFR	94	95	94	111
ALT	45	47	35	74
AST	40	35	36	50
Total bilirubin, mg/dL	3.7	4.3	6	7.8
Direct bilirubin, mg/dL	3.2	3.8	5.1	6.5
CRP, g/L	0.221	0.313	0.225	0.151
PCT, µg/L	3.76	4.62	6.34	2.4
ESR, mm/h	25	42		
Ferritin, ng/mL	626	1351	1573	1343
D-dimer, mg/dL	2.45	2.62	2.76	2.74
Fibrinogen, g/L	7.1	7.45	8.06	4.19
INR	1.64	1.46	1.55	1.15
IL-6, pg/mL	1138	985	945	719
Triglyceride, mg/dL		3.9	3.5	
H-score				219
HLH-2004				6

WBC: White blood cell; GFR: Glomerular filtration rate; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C reactive protein; PCT: Procalcitonin; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; INR: International normalized ratio.

negative. Although the patient's respiratory symptoms were improving, his general condition progressively deteriorated. Neurological symptoms and the complaints of fatigue, loss of appetite and weakness increased. Infection or another reason could not be found to explain his worsening. Elevated C-reactive protein (CRP), ferritin, and triglyceride level, the presence of cytopenia and hepatosplenomegaly led to the suspicion of COVID-19-induced HLH. Laboratory values of the patient are shown in detail in Table 1. On the sixth day of his admission, bone marrow aspiration/biopsy was performed, and it was observed that the bone marrow was infiltrated by activated macrophages in accordance with HLH (Figure 1). The patient's H-Score was calculated at 209, predicting the probability of HLH at 93-96% and calculated HLH-2004 criteria met HLH [7,8]. Valid diagnostic HLH-2004 and H-Score criteria, patient parameters within these criteria, points assigned to the patient based on the parameters within the criteria, and patient's total points for HLH-2004 and H-Score are shown in Table 2. We did not detect any underlying disease triggering HLH except for COVID-19 in detailed analysis. The final diagnosis was accepted as COVID-19-induced HLH for the patient who experienced COVID-19 infection one month ago and had a positive COVID-19 antibody (IgM and IgG). The patient was given pulse steroid therapy (methylprednisolone 2 g/day for 3 days) and intravenous immunoglobulin (IVIG) (2 mg/kg dose, divided into 5 days) in accordance with the HLH-2004 protocol. After pulse steroid therapy, maintenance steroid treatment at a dose of methylprednisolone 1 mg/kg/day was given and ended within 6 weeks. Then plasma exchange treatment was started on the patient on the eleventh day of treatment and applied during the following 4 days. After this treatment, the clinical

Table 2. Valid diagnostic HLH-2004 and H-Score criteria, patient parameters within these criteria, points assigned to the patient based on the parameters within the criteria.

HScore Parameters	HScore Points	Patient's Points	HLH-2004 Parameters	HLH-2004 Points	Patient's Point
Fever, °C					
< 38.4	0		<38.5	0	
38.4-39.4	33		≥ 38.5	1	1
> 39.4	49	49			
Hepatomegaly (HM), splenomegaly (SM)					
None	0			0	
HM or SM	23			1	
HM and SM	38	38		1	1
Known immunosuppression			---		
No	0	0			
Yes	18				
Cytopenia [a,b]					
1 lineage	0			0	
2 lineages	24	24		1	1
3 lineages	34			1	
Ferritin, g/l					
<2.000	0	0	<500	0	
2.000-6.000	35		≥ 500	1	1
> 6.000: 50	50				
Fibrinogen, g/L					
> 2.5	0	0	>1.5	0	0
≤ 2.5	30		≤ 1.5	1	
Triglyceride, mg/dL					
<1.5	0		<3	0	0
1.5-4	44	44	≥ 3	1	
> 4	64				
Aspartate aminotransferase, U/L			---		
< 30					
≥ 30	19	19			
Hemophagocytosis in bone marrow					
No	0			0	
Yes	35	35		1	1
Total points [c]		219			6

a: H-Score: Defined as hemoglobin 92 g/L or less, platelets 110 × 10^9/L or less, and leukocytes 5 × 10^9/L or less 1.0 × 10^9/L; b: HLH-2004: Defined as hemoglobin less than 90 g/L, platelets less than 100 × 10^9/L, and neutrophils less than 1.0 × 10^9/L; c: An H-Score of ≥ 169 has a 93% sensitivity and 86% specificity for HLH.

condition and laboratory values of the patient significantly improved, and the patient was discharged with full recovery at the end of three weeks. The clinical course and consecutive laboratory tests of the patient are shown in Figure 2 and Figure 3.

Review of other COVID-19 associated HLH cases

We conducted a literature review and investigated precisely diagnosed adult HLH cases. Child cases (16 years old and younger), and suspected or unproven HLH cases were not included in the study. We found 21 more adult cases diagnosed with COVID-19-associated HLH in addition to ours [9-19]. Eighteen (86%) of the patients were over the age of 50 (range 17-84), 16 (76%) were male, and most of them had at least one underlying disease. All patients whose medical records were clearly described in the article had a history of fever. The patients were mostly treated with interleukine-1 receptor antagonist (anakinra), interleukin-6 receptor antibody (tocilizumab) and steroid treatment. Nine of them (43%) had died, and 2 were still on mechanical ventilation when the article was written. The characteristics, treatments and outcomes of the patients are shown in Table 3.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

Discussion

Secondary HLH is caused by a group of different reasons such as infections, malignancy, collagen tissue diseases, tissue damage, autoimmune diseases, drugs, metabolites and immunosuppression [20]. Viral infections, especially EBV, CMV, herpes simplex viruses, and other infections such as tuberculosis, malaria, and leishmaniosis can trigger hemophagocytosis [3]. COVID-19 cause a wide range of clinical spectrum from mild disease to severe infection resulting in cytokine storm. An increasing amount of clinical data indicate that cytokine storm plays an important role in the progression to severe infection resulting in acute respiratory distress syndrome (ARDS), and multi-organ failures including heart, kidney, and liver, and eventually death [21-23]. The clinical appearance of SARS-CoV-2 induced cytokine release syndrome has significant similarities with HLH in terms of laboratory and clinical findings. The findings of fever, cytopenia, ARDS, neurological involvement, and renal failure found in patients with severe COVID-19 are the findings that at the same time overlap with HLH [3]. Therefore, HLH should be kept in mind in patients with rapid clinical and laboratory progression to multisystemic severe disease.

Figure 2. Timeline of clinical course of the patient with hemophagocytic lymphohistiocytosis secondary to COVID-19.

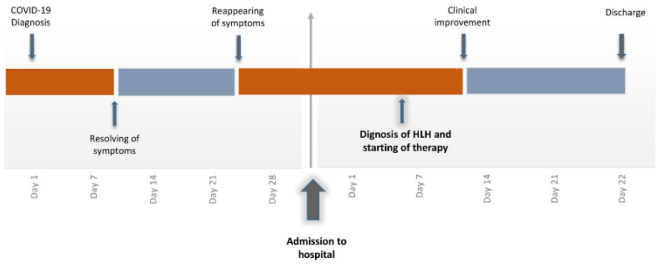
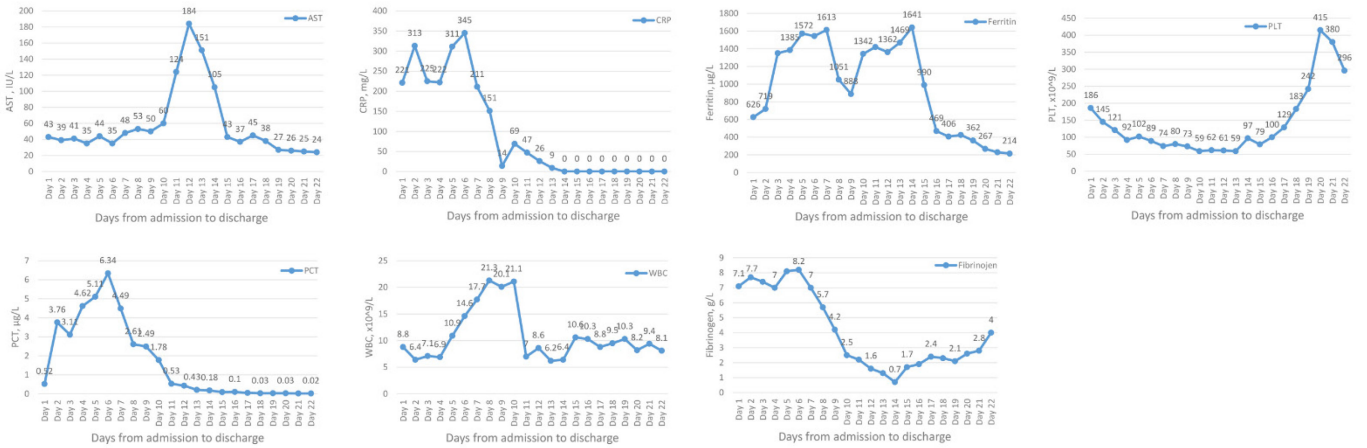


Figure 3. Timeline of laboratory parameters of the patient from admission to discharge.



AST: Aspartate aminotranspherase; CRP: C-reactive protein; PCT: procalcitonin; WBC: White blood cell count; PLT: platelet.

Table 3. The clinical and laboratory characteristics, treatment and outcomes of COVID-19 induced HLH cases reported in the literature.

Patients	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Author	Haigh K et al.	Prilutskiy A et al.	Radbel J et al	Radbel J et al	Adrogué A.H.	von der Thüsen JH et al.	Stanislas Faguer	Lima R et al.	Tholin B et al	Debligus A et al.
Country	United Kingdom	USA, Boston	New Brunswick, NJ	New Brunswick, NJ	USA	Netherlands	France	Brazil	Norway	France
Age	17	72	40	69	53	66	51	60	70	63
Sex	Male	Male	Male	Female	Male	Male	Male	Female	Male	Male
Underlying disease	None	N/A	None	DM, RA, aplastic anemia	Kidney transplantation, HT, DM, CAD	HT, TIA, PAD, polycythemia	Kidney transplantation	DM, HT	Diverticulosis, prostate cancer	N/A
Symptoms and symptoms duration	Fever, cough, sore throat, anorexia (6 days)	Fever	Fever, dry cough, dyspnea (5 days)	Fever, productive cough, abdominal pain (6 days)	Fever, headache, dry cough, myalgia	Fever, dyspnea,	Fever, cough, dyspnea	Fever, dry cough, dyspnea, prostration	Fever, diarrhea, abdominal pain (10 days)	Fever, cough, dyspnea, worsening of general condition
Organomegaly	Cervical LAP, SM	Mediastinal and pulmonary LAP	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-
COVID-19 diagnosis	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR
Elevated transaminase	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	N/A	Yes
Ferritin, µg/l	8.197→ ~10.000	7.679	1.385→ 38.299	2.052→40.934	1.707→4.466	N/A	>6.000→52.000	6.180	544→75.920	4.899
HScore	220	217	Confirmed HLH[&]	Confirmed HLH[&]	165	180	253	Confirmed HLH[&]	Confirmed HLH[&]	207
Hemophagocytosis in BM aspiration/biopsy	Reactive bone marrow	- *	N/A	N/A	Not done	Not done	Yes	Yes	Yes	Yes
COVID-19 treatment	N/A	HQ	HQ and azithromycin	HQ and azithromycin	HQ and azithromycin	N/A	N/A	HQ and azithromycin	HQ and lopinavir-ritonavir	N/A
HLH treatment	Anakinra 100 mg/day, IVIG (2 days)	Anakinra	Tocilizumab, 400 mg	Tocilizumab, 560 mg and tocilizumab 700 mg	-	-	Tocilizumab 8 mg/kg, once	Tocilizumab 400 mg, IVIG, IV hydrocortisone,	Tocilizumab 800 mg	N/A
Complication	N/A	N/A	Viral myocarditis	Acute kidney injury	N/A	Acute kidney injury, multi-organ failure	Heart failure, kidney injury	Acute kidney injury	Monoclonal B-cell lymphocytosis	N/A
Outcome	Alive	Death	Death	Death	Alive	Death	Alive	Death	Alive	Death
Hospitalization time, days	11	4	7	5	12	8	30	12	19	N/A

HLH: Hemophagocytic lymphohistiocytosis; DM: diabetes mellitus; RA: rheumatoid arthritis; HT: hypertension; TIA: trans ischemic attack; CAD: coroner arterial disease; PAD: peripheral arterial disease; HQ: hydroxychloroquine; PCR: polymerase chain reaction; LAP: lymphadenopathy; HM: hepatomegaly; SM: splenomegaly; BM: bone marrow; N/A: None-available; [&:] HLH diagnosis was reported to be confirmed in the article; * Hemaphagocytosis in lymph node.

Table 3 (continued). The clinical and laboratory characteristics, treatment and outcomes of COVID-19 induced HLH cases reported in the literature

Parameters	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18	Patient 19	Patient 20	Patient 21
Author	Perieto-Perez L et al.	Perieto-Perez L et al.	Perieto-Perez L et al.	Dimopoulus G et al.	Dimopoulus G et al.	Dimopoulus G et al.	Dimopoulus G et al.	Dimopoulus G et al.	Dimopoulus G et al.	Dimopoulus G et al.	Dimopoulus G et al.
Country	Spain	Spain	Spain	Greece	Greece	Greece	Greece	Greece	Greece	Greece	Greece
Age	60	70	45	51	74	67	84	56	68	67	71
Sex	Male	Female	Female	Male	Male	Male	Male	Male	Male	Male	Female
Underlying disease	AML M5b	AF, asthma, colorectal cancer, CRD	Follicular lymphoma	Arterial hypertension	DM, HT, BPH	CHD, HT, dyslipidemia,	CHD, COPD, BPH, dyslipidemia	HT	DM, CHD, dyslipidemia, HT, stroke	DM, CHD, dyslipidemia, HT, stroke	HT, dyslipidemia, colon Ca
Symptoms and symptoms duration	N/A	N/A	N/A	Fever	Fever	Fever	Fever	Fever	Fever	Fever	Fever
Organomegaly	N/A	N/A	SM	-	HM, SM	HM, SM	SM	HM	HM, SM	HM, SM	-
COVID-19 diagnosis	PCR	PCR	PCR	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Elevated transaminase	N/A	N/A	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ferritin, µg/l	2932	16248	2288	5002	1924	3582	6032	6786	7389	10500	>6000
HScore	Confirmed HLH	Confirmed HLH[&]	Confirmed HLH[&]	171	170	169	178	185	171	218	198
Hemophagocytosis in BM aspiration/biopsy	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
COVID-19 treatment	N/A	N/A	N/A	HQ	HQ	HQ	HQ	HQ	HQ	HQ	N/A
HLH treatment	N/A	N/A	N/A	Anakinra, hydrocortisone 50mg 6qh x7 days IV	Anakinra, hydrocortisone 50mg 6qh x7 days IV	Anakinra, hydrocortisone 50mg 6qh x7 days IV	Anakinra	Anakinra	Anakinra	Anakinra	Anakinra
Complication	N/A	N/A	N/A	Refractory shock	Refractory shock, bacteremia	N/A	Refractory shock, acute kidney injury	N/A	N/A	N/A	N/A
Outcome	Alive	Alive	Alive	Death	Death	Alive	Death	Alive	Alive	Alive	Alive
Hospitalization time, days	N/A	N/A	N/A	12	9	Weaning from MV day 22	19	Weaning from MV day 31	on MV	on MV	9

HLH: hemophagocytic lymphohistiocytosis; AML: acute myeloid leukemia; AF: atrial fibrillation; CRD: chronic renal disease; HT: hypertension; DM: diabetes mellitus; CHD: chronic heart disease; COPD: chronic obstructive pulmonary disease; BPH: benign prostate hyperplasia; HQ: hydroxychloroquine; PCR: polymerase chain reaction; HM: hepatomegaly; SM: splenomegaly; BM: bone marrow; N/A: None-available; [&:] HLH diagnosis was reported to be confirmed in the article.

Hyperinflammatory syndromes and its impact on mortality have gained a foothold in the literature about COVID-19 pathogenesis. Various types of proinflammatory cytokines and chemokines are released at different levels and cause a heterogeneous clinical severity, from mild disease to severe disease reminiscent of secondary HLH. Cytokine levels are higher in severe COVID-19 patients than non-severe patients [23-25]. A recent study reported a cytokine profile associated with increased disease severity in COVID-19 patients that is similar to HLH cases [26]. Laboratory abnormalities (eg cytopenia, elevated CRP, interleukin-6 (IL-6), ferritin, and D-dimer) are more commonly detected in severe cases of COVID-19 [26,27]. Patients with rapid and progressive laboratory deterioration may be suffering from excessive cytokine production. Therefore, HLH criteria should be investigated in COVID-19 patients who are acutely ill or have a deteriorating clinic and deepening laboratory abnormalities. A recent review by Opoka-Winiarska *et al.* recommends investigating HLH criteria in all COVID-19 patients with worsening of general condition and multi-organ failure [5]. Timely diagnosis and starting appropriate treatment for HLH play an important role in prognosis.

Male gender was dominant in HLH cases associated with COVID-19 in published articles. Similar to COVID-19 cases, a slight predominance of male gender was also reported in non-COVID-19 associated HLH cases [28]. In fact, male dominance in HLH cases sounds reasonable, because male gender was reported as a poor prognostic factor for severe COVID-19 infection in multiple cohorts worldwide [29-31]. Most of the COVID-19 associated HLH patients were older than 50 years old. This was also compatible with the results of COVID-19 cohorts in which advanced age was reported as a risk factor for mortality [25-27].

Primary HLH seen in childhood, also called familial HLH, has a genetic inheritance and is caused by various mutations in the gene encoding perforin (PRF). There is a dysregulation in the immune system due to the perforin-mediated cell lysis pathway that results in over-activation of cytotoxic CD8+ T cells, natural killer cells, and macrophages of activated cells. The primary HLH emerges typically during early infancy and causes death within two months if left untreated. The diagnosis is established with a molecular test consistent with HLH [3,7]. There is no confirmatory test for the diagnosis of secondary HLH, and clinical and laboratory tests are mainly used [3]. Most patients with HLH experience acute multiorgan insufficiency including cytopenia, liver test abnormalities, coagulopathy and neurological symptoms which cannot be explained with any other reasons. HLH-2004 diagnostic guideline developed by Histiocyte Society and H-Score are criteria that are widely used to help diagnosis in children [7,8]. Diagnostic HLH-2004 contains eight criteria and the presence of five of the eight criteria is required to meet the HLH criteria. Nine variables (3 clinical, 5 laboratory and a cytological) are used for H-Score and the possibility are changed according to the total score. In fact, the detection of hemophagocytosis in bone marrow aspiration is neither necessary nor sufficient for diagnosis, it is only one of the criteria included in diagnostic scores. Hemaphagocytosis may not be detected in the early period in bone marrow due to a late period's finding of HLH [32,33]. Hemophagocytosis had reportedly been detected in bone marrow samples of all patients who were included in this study and who underwent bone marrow aspiration. Therefore, bone marrow aspiration / biopsy should be performed in patients with suspected HLH, especially in patients who are at the margin of diagnosis. Although hemophagocytosis cannot be detected in bone marrow aspiration, patients with suspected HLH should receive HLH-specific treatment without wasting time, preferably on the day of diagnosis. The effectiveness of the treatment depends on its timing; its early initiation improves the response and prognosis [5,7]. The initial therapy aims to suppress hyperinflammation by immunosuppressive treatment. HLH-2004 guideline recommends starting initial treatment immediately after ruling out lymphoma. HLH is a severe kind of hyperinflammatory syndrome, and its main treatment is obtained by the suppression of cytokine. Corticosteroid is the first preferable drug in treatment of infection associated HLH and often used in combination with IVIG [5,7,34]. It is recommended that plasma exchange therapy may be performed to improve coagulation test and eliminate cytokines [34]. We started corticosteroid and IVIG combination treatment on the day of diagnosis, and applied plasma exchange after five days of combination treatment. The patient responded very well to the treatment with early diagnosis and appropriate treatment. In COVID-19 associated HLH cases included in this study, anakinra and tocilizumab had been widely used. Anakinra is used with other immunosuppressive drugs in the treatment of hemophagocytic syndrome and associated with an improved response, and tocilizumab is reported to be effectively used in the treatment of cytokine release syndrome, especially following chimeric antigen receptor (CAR)-T cell therapy. However, there is insufficient evidence to recommend for or against the

use of both cytokine-inhibiting agents, anakinra and tocilizumab, in cytokine storm during COVID-19 infection. [3,25,35-37].

Conclusions

Hyperinflammatory syndromes are well-defined COVID-19-associated clinical conditions and may exhibit a wide range of diversity. HLH is a rarely seen, acute progressive hyperinflammatory syndrome and may accompany COVID-19. It may be overlooked due to a rapid clinical progression resulting in multiorgan failure. Early diagnosis of HLH and starting of appropriate treatment can be life-saving in patients with deteriorating general conditions. There is no specific confirmatory test for the diagnosis of adult HLH cases. HLH-2004 and H-Score guidelines can be used to help the diagnosis of HLH. Hemophagocytosis in bone marrow may not be detected at an early stage and is not required for precise diagnosis. Specific treatment should be initiated in patients with high clinical suspicion without wasting time.

References

1. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, Komanduri KV, Lin Y, Jain N, Daver N, Westin J, Gulbis AM, Loghin ME, de Groot JF, Adkins S, Davis SE, Rezvani K, Hwu P, Shpall EJ (2018) Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol 15: 47-62.
2. George MR (2014) Hemophagocytic lymphohistiocytosis: review of etiologies and management J Blood Med 5: 69-86.
3. Soy M, Atagunduz P, Atagunduz I, Sucak GT (2020) Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. Rheumatol Int 41: 7-18.
4. McGonagle D, Sharif K, O'Regan A, Bridgewood C (2020) The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmun Rev 19: 102537.
5. Opoka-Winiarska V, Grywalska E, Rolinski J (2020) Could hemophagocytic lymphohistiocytosis be the core issue of severe COVID-19 cases? BMC Med 18: 214.
6. Debliquis A, Harzallah I, Mootien JY, Poidevin A, Labro G, Mejri A, Lamarque M, Kuteifan K, Drénou B (2020) Haemophagocytosis in bone marrow aspirates in patients with COVID-19. Br J Haematol 190: e70-e73.
7. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G (2007) HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 48: 124-131.
8. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan Coppo P, Hejblum G (2014) Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol 66: 2613–2620.
9. Haigh K, Syrimi ZJ, Irvine S, Blanchard TJ, Pervaiz MS, Toth AG, Ratcliffe L (2020) Hyperinflammation with COVID-19: The key to patient deterioration? Clin Infect Pract 24: 100033.
10. Prilutskiy A, Kritselis M, Shevtsov A, Yambayev I, Vadlamudi C, Zhao Q, Kataria Y, Sarosiek SR, Lerner A, Sloan JM, Quillen K, Burks EJ (2020) SARS-CoV-2 Infection-Associated Hemophagocytic Lymphohistiocytosis. Am J Clin Pathol 154: 466-474.
11. Radbel J, Narayanan N, Bhatt PJ (2020) Use of Tocilizumab for COVID-19-Induced Cytokine Release Syndrome: A Cautionary Case Report. Chest 158: e15-e19.
12. Adrogué AH, Mithani F, Ibrahim HN, Schwartz MR, Gaber L, Hebert SA, Adrogué HE (2020) A Kidney Transplant Recipient With Coronavirus Disease 2019: Utility of a Prognostication Score. Transplant Proc 52 (9): 2688-2692.
13. von der Thüsen JH, van Bommel J, Kros JM, Verdijk RM, Lopuhaä B, Lam KH, Dik WA, Miedema JR (2020) Case report: a fatal combination of hemophagocytic lymphohistiocytosis with extensive pulmonary microvascular damage in COVID-19 pneumonia. J Hematop 23: 1-5.
14. Faguer S, Del Bello A, Abravanel F, Nicolau-Travers ML, Kamar N (2020) Tocilizumab for Hemophagocytic Syndrome in a Kidney Transplant Recipient With COVID-19. Ann Intern Med 173: 501-503.
15. Lima R, Filho CC, Ferreira Filho CM, Vaisman M, Cossenza A, Rebello CP, Leite CA, de Oliveira Tavares D, Ramalho JF (2020) Hemophagocytic syndrome and COVID-19. Respir Med Case Rep 31: 101162.
16. Tholin B, Hauge MT, Aukrust P, Fehrle L, Tvedt TH (2020) Hemophagocytic lymphohistiocytosis in a patient with COVID-19 treated with tocilizumab: a case report. J Med Case Rep 14: 187.
17. Debliquis A, Harzallah I, Mootien JY, Poidevin A, Labro G, Mejri A, Lamarque M, Kuteifan K, Drénou B (2020) Haemophagocytosis in bone marrow aspirates in patients with COVID-19. Br J Haematol 190: e70-e73.
18. Prieto-Perez L, Fortes J, Soto C, Vidal-González A, Alonso-Riano M, Lafarga M, Cortti MJ, Lazaro-Garcia A, Perez-Tanoira R, Trascasa A, Antonio A, Cordoba R, Rodriguez-Pinilla SM, Cedeno O, Peces-Barba G, Fernandez-Ormaechea I, Diez Medrano MJ, Lopez de Las Heras M, Cabello A, Petkova E, Alvarez B, Carrillo I, Silva AM, Castellanos M, Calpena S, Valverde-Monge M, Fresneda D, Rubio-Martin R, Cornejo I, Astilleros Blanco de Cordova L, de la Fuente S, Recuero S, Górgolas M, Piris MA (2020) Histiocytic hyperplasia with hemophagocytosis and acute alveolar damage in COVID-19 infection. Mod Pathol 33: 2139-2146.
19. Dimopoulos G, de Mast Q, Markou N, Theodorakopoulou M, Komnos A, Mouktaroudi M, Netea MG, Spyridopoulos T, Verheggen RJ, Hoogerwerf J, Lachana A, van de Veerdonk FL, Giamarellos-Bourboulis EJ (2020) Favorable Anakinra Responses in Severe Covid-19 Patients with Secondary Hemophagocytic Lymphohistiocytosis. Cell Host Microbe 28: 117-123.e1.
20. Janka GE (2007) Familial and acquired hemophagocytic lymphohistiocytosis. Eur J Pediatr 166: 95-109.
21. Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G (2020) COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. Cytokine Growth Factor Rev 53: 66-70.
22. Chousterman BG, Swirski FK, Weber GF (2017) Cytokine storm and sepsis disease pathogenesis. Seminars Immunopathol 39: 517-528.

23. Ye Q, Wang B, Mao J (2020) The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect 80: 607-613.
24. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. (2020) Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 71: 762-768.
25. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S (2020) Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol 39: 2085-2094.
26. Huang C, Wang Y, Li X, Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497-506.
27. Güner R, Hasanoğlu I, Kayaaslan B, Aypak A, Kaya Kalem A, Eser F, Ozdemir B, Sarıcaoglu EM, Ayhan M, Aybar Bilir Y, Ozkocak Turan I, Erdem D, Mutlu NM, Buzgan T, Dinc B, Akınci E (2020) COVID-19 experience of the major pandemic response center in the capital: Results of the pandemic's first month in Turkey. Turk J Med Sci 50: 1801-1809.
28. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X (2014) Adult haemophagocytic syndrome. Lancet 383: 1503-1516.
29. Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J (2020) Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Crit Care 24: 108.
30. Cunningham JW, Vaduganathan M, Claggett BL, Jering KS, Bhatt AS, Rosenthal N, Solomon SD (2020) Clinical Outcomes in Young US Adults Hospitalized With COVID-19. JAMA Intern Med 181: 379-381.
31. Richardson S, Hirsch JS, Narasimhan M, rawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP (2020) Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 323: 2052-2059.
32. Goel S, Polski JM, Imran H (2012) Sensitivity and specificity of bone marrow hemophagocytosis in hemophagocytic lymphohistiocytosis. Ann Clin Lab Sci 42:21–5.
33. Ho C, Yao X, Tian L, Li FY, Podoltsev N, Xu ML (2014) Marrow assessment for hemophagocytic lymphohistiocytosis demonstrates poor correlation with disease probability. Am J Clin Pathol 141: 62-71.
34. Morimoto A, Nakazawa Y, Ishii E (2016) Hemophagocytic lymphohistiocytosis: Pathogenesis, diagnosis, and management. Pediatr Int 58: 817-825.
35. Wohlfarth P, Agis H, Gualdoni GA, Weber J, Staudinger T, Schellongowski P, Robak O (2019) Interleukin 1 Receptor Antagonist Anakinra, Intravenous Immunoglobulin, and Corticosteroids in the Management of Critically Ill Adult Patients With Hemophagocytic Lymphohistiocytosis. J Intensive Care Med 34: 723-731.
36. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini G, Antinori S, Galli M (2020) COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol 38: 337–342
37. England JT, Abdulla A, Biggs CM, Lee AYY, Hay KA, Hoiland RL, Wellington CL, Sekhon M, Jamal S, Shojania K, Chen LYC (2020) Weathering the COVID-19 storm: Lessons from hematologic cytokine syndromes. Blood Rev 15: 100707.

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Conflict of interests: No conflict of interests is declared.