

## “Covid-19 A New Viral Trigger to Hemophagocytic Lymphohistiocytosis?”

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## 1. Summary

We report a case of patient with COVID-19 pneumonia who had prolong course in critical care unit and developed clinical and laboratory features of Hemophagocytic Lymphohistiocytosis (HLH) supported by findings on bone marrow. Patient received supportive treatment and IL-6 inhibitor but developed multiorgan failure and could not revive back to life. HLH is life threatening condition with rapid course and can lead to multiorgan failure and death. This case highlights the importance of fact that HLH can lead to significant morbidity and mortality in critically ill patient with COVID-19 pneumonia and it warrants early evaluation in these patients.

## 2. Introduction

Nearly 4.2 million [1] people are affected by Coronavirus (SARS-CoV-2 or COVID-19) worldwide since the new virus emerged in

china late in 2019.

Although the majority of patients are suffering from mild disease, a significant number of patients still requires intensive care management [2]. It is not clear yet why the virus manifests itself as life threatening and deadly in some patients. Whether the direct viral infection or the abnormal hyperimmune response is the main cause of mortality is still an area of ongoing research.

Secondary Hemophagocytic Lymphohistiocytosis (HLH) is one such example of life threatening and excessive immune activation leading to tissue destruction and multiorgan failure [3]. HLH has been described in the past in association with rheumatological disorders [4, 5] and certain viral infections such as Epstein-Barr virus (EBV) [5].

Various scores have been validated for the prediction of HLH in clinically relevant context. One such score is the H score [6] as summarized in (Table 1).

Table 1: The Hscore [8]

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression <sup>a</sup>	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No. of cytopenias <sup>b</sup>	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (ng/ml)	0 (<2,000), 35 (2,000–6,000), or 50 (>6,000)
Triglyceride (mmoles/liter)	0 (<1.5), 44 (1.5–4), or 64 (>4)
Fibrinogen (gm/liter)	0 (>2.5) or 30 (≤2.5)
Serum glutamic oxaloacetic transaminase (IU/liter)	0 (<30) or 19 (≥30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)

<sup>a</sup> Human immunodeficiency virus positive or receiving long-term immunosuppressive therapy (i.e., glucocorticoids, cyclosporine, azathioprine).

<sup>b</sup> Defined as a hemoglobin level of ≤9.2 gm/dl and/or a leukocyte count of ≤5,000/mm<sup>3</sup> and/or a platelet count of ≤110,000/mm<sup>3</sup>.

In this case presentation, we describe a patient with COVID-19 whose disease course was complicated by a hyperimmune state most suggestive of secondary HLH.

### 3. Case Presentation

The patient was 56-year old gentleman who presented with 7 days of fever, cough and body pain on the 21<sup>st</sup> March 2020. He has a history of hypertension and was taking telmisartan for blood pressure control.

On initial evaluation, the patient was febrile with a temperature of 38.1 C but otherwise hemodynamically stable with no signs of respiratory distress. Initial laboratory investigations revealed normal complete blood count, renal function and liver function. Chest X-Ray was reported as normal. Nasopharyngeal PCR was positive for COVID 19.

Patient was discharged after 3 days with strict home isolation.

The patient was re-admitted to the hospital again 2 days after discharge with persistent fever and shortness of breath. Reassessment revealed ongoing fever with a temperature of 38.2, tachypnea with RR of 25/min, SaO<sub>2</sub> of 91% on room air, blood pressure of 104/75 and heart rate of 81 per minute. Chest auscultation revealed crepitations over both lung bases and chest X-Ray showed bilateral lower lung zones/perihilar infiltrates/patchy opacities (Figure 1-A). Laboratory investigations showed lymphopenia with a lymphocyte count of  $0.9 \times 10^3/\mu\text{L}$ , increase in ALT and AST (121 U/L and 126 U/L respectively), elevated C Reactive Protein (CRP) of 207.6 mg/L and elevated ferritin value of 3,191  $\mu\text{g/L}$ .

Patient was started on a treatment as per the local protocols for COVID-19 pneumonia which includes azithromycin, hydroxychloroquine, Darunavir/cobicistat, oseltamivir, enoxaparin 40mg subcut daily and antibiotics.

On day 2 of hospital stay, patient was shifted to intensive care

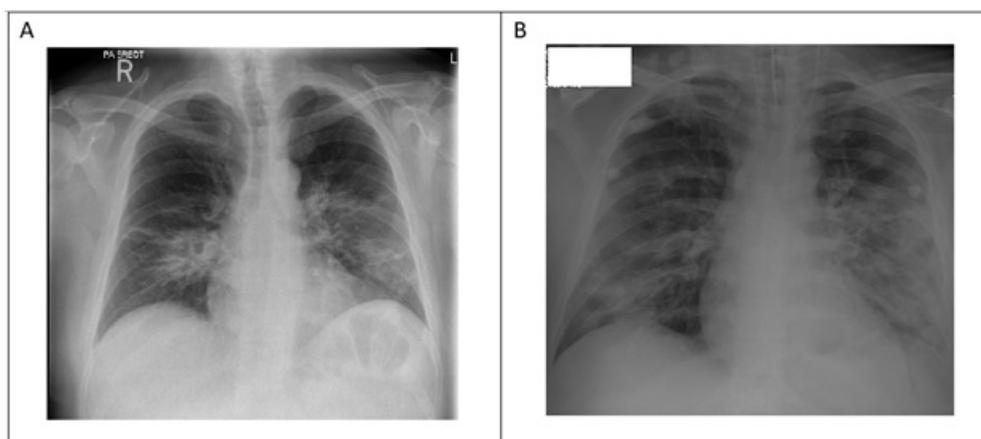
unit due to respiratory distress with a respiratory rate of 32 and oxygen saturation of 88%. Oxygen therapy through face mask and later on trial of CPAP failed to improve patient oxygenation and patient was intubated on day 3 of hospitalization. Antibiotics coverage was changed to tazocin and patient was started on ribavirin 1.2 gm twice daily, peginterferon alfa-2a 180 mcg subcutaneously once weekly, methylprednisolone 40mg IV twice daily for 5 days and received one dose of tocilizumab 400mg IV. Patient was on continuous mechanical ventilation but was not showing significant signs of improvement and failed multiple attempts to wean him off ventilation. On day 15, patient deteriorated further and became hemodynamically unstable with a temperature of 40.2 °C, oxygen saturation of 80% and blood pressure of 80s/50s requiring vaso-pressors. Repeat chest X-Ray on day 16 is showed in (Figure 1-B).

(Table 2) summarized the sequence of changes in laboratory parameters from day 15 to day 20 of hospitalization.

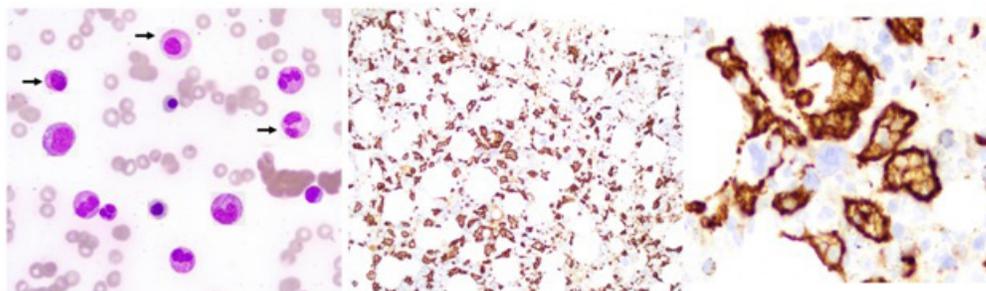
Patient developed acute kidney injury requiring renal replacement therapy. In view of changing laboratory parameters and very high ferritin level with a high H score patient was started on treatment for cytokine storm and secondary HLH with IV immunoglobulins and another dose of tocilizumab 600mg intravenously. He underwent bone marrow aspiration and biopsy on day 18 which confirmed the presence of prominent histiocytes/macrophages (positive for CD68/CD163IHC) with evidence of hemophagocytosis (Figure 2).

Head CT revealed bilateral frontal intra-axial hematomas associated with subarachnoid hemorrhage, intraventricular hemorrhage, and diffuse brain edema with subfalcine brain herniation.

Patient's condition continued to rapidly decline with loss of all brain stem reflexes. Patient arrested and died on day 24 of hospitalization.



**Figure 1:** Patient's chest X-Ray images A) on admission to the ICU showing bilateral lower lung zones/perihilar infiltrates and patchy opacities and B) on day 16 showing ill-defined patchy and fluffy opacities, partially coalescing, within both lungs more in the left indicating massive parenchymal inflammatory infiltrates.



**Figure 2.** Bone marrow aspirate (A) and biopsy (B and C) slides showing A) different stages of granulocytic cells with some dysplastic non-segmented or hypo-segmented neutrophils (arrows) with erythroid precursors and rare lymphocytes on wright stain x1000, B) increased histiocytes/macrophages as highlighted by CD163 immunostaining x200, and C) histiocytes with haemophagocytosis.

**Table 2.** Laboratory parameter of patients from week 3 onward.

	Day 15	Day 16	Day 18	Day 20
WBC 10 <sup>3</sup> /uL	12.8	29.5	26.5	31.4
Hb gm/dL	14.6	12.1	7.5	6.5
Plt 10 <sup>3</sup> /uL	225	56	21	53
Fibrinogen gm/L	2.8	0.8	0.9	1.8
D-Dimer mg/L	10.97	27.06	14.14	6.11
Triglyceride mmol/L		10.4	9.2	
Ferritin ug/L	4026	>100000	>100000	67895
ALT U/L	54	2845	3093	1192
AST U/L	45	2683	2122	546
LDH U/L	579			1547
Creatinine umol/L	62	241	437	325
H score	212 <sup>a</sup>		271 <sup>b</sup>	

<sup>a</sup> H score without bone marrow aspirate.

<sup>b</sup> H score including bone marrow aspirate findings.

#### 4. Discussion

Patients with HLH are critically ill with a clinical presentation that is no different than septic shock with multiple organ failure. Lung involvement with development of adult respiratory distress syndrome (ARDS), liver abnormalities, neurologic involvement, cytopenia, coagulation abnormalities with DIC and a state of shock requiring vasopressors are among the fatal clinical manifestations of HLH.

Clinical, laboratory parameters and evidence of hemophagocytosis on bone marrow examination help reach a diagnosis of HLH. The H score can be calculated quickly and can help predict the development of HLH when clinically suspected.

Different Viruses are reported to cause secondary HLH e.g Epstein-Barr virus (EBV)<sup>7</sup>, influenza A<sup>8</sup> and other strains of coronavirus SARS-Coronavirus Cov and MERS-CoV [9, 10].

Here, we present a case of HLH syndrome in association with confirmed COVID-19 infection. He was initially put on ventilatory support for respiratory failure but developed a shock-like state during the 3<sup>rd</sup> week of ICU stay, manifested by hypotension, ARDS and worsening respiratory failure, acute liver and renal injury, cytopenia, DIC and abnormal laboratory parameters suggestive of HLH. Bone marrow aspirate confirmed hemophagocytosis and the diagnosis of HLH. Despite supportive measures and immunosup-

pressive therapy, patient's condition continued to rapidly deteriorate and was complicated by intracranial bleeding most likely due to DIC leading to death of multi-organ failure.

It is, therefore, critical to consider and evaluate for HLH in patients with COVID19 infection who show signs of clinical deterioration and multi-organ failure.

#### 5. Conclusion

HLH can be a cause of critical and life-threatening illness in patient with COVID-19 pneumonia and can lead to multi-organ failure and death. It should be considered early in the differential diagnosis of critically ill COVID-19-infected patients in order to obtain the necessary investigations to confirm the diagnosis and apply the therapeutic interventions that might save the patient's life.

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