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A Case of Secondary Hemophagocytic Lymphohistiocytosis (sHLH) Induced by a recent Infection of SARS-CoV2

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Abstract

Background: Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and progressive systemic disorder of excessive inflammation and tissue destruction due to abnormal immune activation. In the literature, a few documented cases of COVID-19 patients and HLH with signs of hemophagocytosis in bone marrow aspiration or biopsy. Some authors propose that cytokine storm and immunodeficiency due to infection of Covid 19 lead to the same clinical manifestations and laboratory findings of primary HLH and use the term "Macrophage Activation Syndrome-Like Disease". On the other hand, other authors suggest that infection of COVID-19 can trigger HLH, so it is considered a secondary viral aetiology of sHLH.

Case report: We report a case of a secondary HLH induced by a recent infection of Sars-Covid 19 with a spontaneous and progressive improvement of clinical status, characterized by stable defervescence, improved haematological condition with an increase of haemoglobin and platelets levels, and decreased inflammation markers such as RCP, ESR, IL-6.

Conclusions: Our case report suggests some possible essential and novel issues concerning the correlation between infection of COVID-19 and insurgence of HLH with a documented sign of hemophagocytosis in bone marrow aspiration. It, therefore, addresses the thorny question, based on current knowledge, of finding the pathogenesis of secondary haemophagocytic syndrome, i.e. whether it is caused by the viral infection per se or whether it depends on the 'second wave inflammation' induced by the dysregulation of the immune system caused by the virus.

Keywords: Secondary Hemophagocytic Lymphohistiocytosis; Covid-19; SARS-Cov-2; Cytokine Storm; Macrophage Activation Syndrome; Case Report.

Abbreviations: HLH: Hemophagocytic lymphohistiocytosis; fHLH: Familiar Hemophagocytic lymphohistiocytosis; sHLH: secondary Hemophagocytic lymphohistiocytosis; MAS: Macrophage Activation Syndrome; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; IL-1,6,18,33; Interleukin-1,6,18,33; CMV: cytomegalovirus, EBV: Epstein-Barr virus; HIV: Human immunodeficiency virus, HBV: Hepatitis B virus; HCV: Hepatitis C virus; TD: transverse diameter; NK: Natural Killer; TNF: tumor necrosis factor; Th1: T helper-1; Th2: T helper-2; Th17: T helper-17; SARS-CoV-2: Severe Acute Respiratory SIndrome by Coronavirus 2.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and rapidly progressive systemic disorder of excessive inflammation and tissue destruction due to abnormal immune activation [1]. It frequently affects children, but the disease is common in adults of all ages. HLH can occur in two different conditions: a primary form, also called Familial HLH (fHLH), due to genetic defects of lymphocyte cytotoxicity, and a secondary form (sHLH) triggered by underlying disorders like viral infections, malignancies, and autoimmune diseases. In particular, macrophage activation syndrome (MAS) is a secondary form of HLH (sHLH) caused by rheumatologic disorders [2]. The macrophage-endothelial system activation causes the cytokine storm, which amplifies and supports the whole mechanism of haemophagocytosis. [1].

HLH is an acute systemic inflammatory disease characterized by various clinical manifestations like recurrent fever, splenomegaly, lymphadenopathy, anemia, thrombocytopenia, encephalitis, seizures, altered liver function, and coagulation abnormalities.

In the literature, a few documented cases of COVID-19 patients and HLH are reported with signs of hemophagocytosis in bone marrow aspiration or biopsy [3]. As far as our knowledge of literature is concerned, there is an ongoing debate regarding the relationship between HLH and viral infection of COVID-19. In this regard, the current literature confirms the existence of a cytokine storm induced by SARS-CoV-2 infection and recognizes its pathogenic role in specific systemic clinical manifestations. What is still unclear, and on which our case report seeks to shed further light, is whether this cytokine storm is the cause of our patient's macrophage activation syndrome, given that in Covid 19 patients, the haemophagocytic syndrome found to have the features of an ARDS, or whether it was due to the viral infection per se [4-6].

Case Presentation

We present a case of a 66-year-old woman with a history of hypertension and chronic coronary syndrome, taking valsartan and aspirin daily. In October 2022, the patient was recovered in another hospital ward for a persistent fever (lasting at least seven days with a T max 39° C°) and symptomatology characterized by ageusia, anosmia, and dyspnea. During the recovery, a chest tomography showed scattered ground-glass areas with interstitial characters, and was performed a COVID-19 nasal swab specimen, resulting in positive. In November 2022, the patient was discharged at home with a diagnosis of SARS-CoV-2 pneumonia, and it was recommended that she practice therapy with clarithromycin, dexamethasone, and heparin (at an unspecified dosage). On 20th November, the COVID-19 nasal swab specimen was finally negative; consequently, the patient stopped the steroid therapy.

In December 2022, the patient was admitted to our ward for prolonged, persistent asthenia and relapsed fever (15 days with a T max 38,5° C°). Vital parameters were normal (blood pressure of 120/85 mmHg, heart rate of 72 bpm, pulse oximeter saturation of 96%, body temperature of 36.9 °C). At the physical examination, she presented splenomegaly, hepatomegaly, and a scattered reduction of vesicular murmur in all lung segments. The laboratory findings showed increased ESR, CRP, IL-6 levels, anemia, thrombocytopenia, hyperferritinemia, and hypertriglyceridemia (Table 1). Furthermore, chest and abdominal tomography showed the initial resolution of COVID-19 pneumonia with ground-glass areas on lower lobes, bilateral basal pleuric effusion, and splenomegaly (20 cm of TD).

These findings raised the suspicion of HLH, so was performed a bone marrow aspiration which showed the presence of "histiocyte with the sign of pinocytosis suggestive for hemophagocytosis and erythroid island sign of medullary recovery, 65% cellularity, presence of CD 68+ elements"(Figure 1). The diagnosis of HLH was based on the presence of five of eight HLH-2004 criteria (Fever, splenomegaly, Bicytopenia, hypertriglyceridemia, hyperferritinemia, and the sign of hemophagocytosis in bone marrow aspiration).

Moreover, secondary causes of HLH like viral infection (CMV, EBV, HIV, HBV, HCV, and Parvovirus B19) and autoimmune disease (negative anti-nuclear antibodies -ANA- and rheumatoid factor) have been excluded; the recent chest and abdominal tomography showed no findings suggestive for malignancies. During the hospitalization, concerning the stability of the patient's clinical condition, we adopted a wait-and-see approach and observed a spontaneous progressive improvement of her clinical status with progressive and stable defervescence, improved hematological condition with an increase of hemoglobin and

platelets levels, and decreased inflammation markers such as RCP, ESR, IL-6; there was no need for either red cells or platelet transfusion or treatment with steroids.

The patient was discharged with the diagnosis of Hemophagocytic lymphohistiocytosis secondary to a recent infection of SARS-Covid-19. During the follow-up period of 6 months, a progressive resolution of the hematological status with the disappearance of anemia and thrombocytopenia was observed. In addition, there was a mild increase in CRP levels, which spontaneously reduced after two weeks of follow-up (Table 1).

	Referral Ranges	Recovery		Follow-Up
		Admission	Discharge	
Hematology				
Total WBC count (x103/mm3)	04-Nov	5.14	5.61	6.18
Neutrophilis (%)	40 - 74	62.9	42.2	62.4
Lymphocytes (%)	20 - 48	28	45.2	23.9
Monocytes (%)	03-Nov	8.9	11.1	11
Eosinophilis (%)	0 - 8	0	0	2.1
Basophilis (%)	0 - 1.5	0	1.2	0.6
Red cell count (x106/mm3)	3.8 - 5	3.1	3.2	3.74
Hemoglobin (g/dL)	Dec-16	6.8	9.1	10
Hematocrit (%)	35 - 48	19	27.6	32.9
Mean cell volume (fl)	80 - 99	73.9	86	88
Platelet count (x103/L)	150 - 450	43	437	270
Inflammatory Mediators				
Erythrocyte sedimentation rate (mm/h)	Oct-20	87	15	66
C-reactive protein (mg/L)	<5	100.93	13	26.42/8.4
Procalcitonin (µg/L)	0.554	1.34	0.04	-
Ferritin (ng/mL)	15 - 150	4081	-	359.9
Fibrinogen (mg/dL)	150 - 450	132	492	-
Liver Function Tests and Lipids				
AST/ALT (IU/L)	0 - 50	39/36	-	-
Lactate dehydrogenase (U/L)	50 - 250	264	120	60
Triglycerides (mg/dL)	< 150	244	-	179
Serologic Tests				
Brucella antibodies		Neg	-	-
Leishmania antibodies		Neg	-	-
Rickettsia antibodies		Neg	-	-
Toxoplasma gondi antibodies		Neg	-	-
CMV antibodies		Neg	-	-
EBV antibodies		Neg	-	-
HIV antibodies		Neg	-	-
HBV antibodies		Neg	-	-
HCV antibodies		Neg	-	-
Human Parvovirus-B19 antibodies		Neg	-	-

Antigen tests				
SARS-CoV 2		Neg	-	Neg

Table 1: Laboratory Findings of Clinical Case.

FIGURE 1

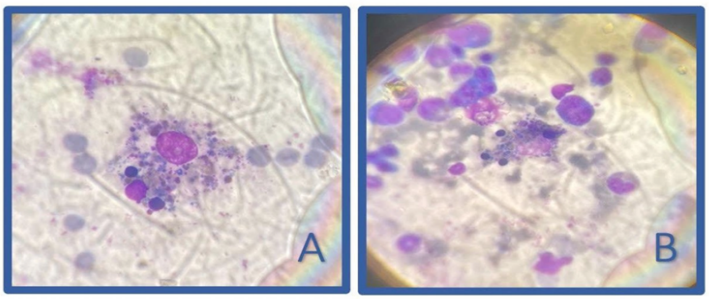

Figure 1: A. Histiocyte with signs of pinocytosis. B. Histiocyte with signs of pinocytosis suggestive of phagocytosis and Erythroid Island indicative of medullary recovery.

Discussion

HLH is a life-threatening disease characterized by excessive activation of macrophages, the inability of NK cells and T-cells CD8+ to eliminate these macrophages, and cytokine storm; this condition leads to cytopenias, especially thrombocytopenia and anemia [7]. HLH can occur in two conditions: a primary form, also called Familiar HLH (fHLH), and a secondary form (sHLH) triggered by an underlying disorder. The primary form of HLH is due to genetic mutations, and the more implicated genes are involved in the perforin-mediated cytotoxicity [8]. This fact could seem contradictory, but it is not: the inability to remove the pathological antigen promotes further inflammation to reinforce the immune system in vain. On the other hand, secondary forms can be triggered by infections, typically viral ones [2], malignancies, and rheumatological diseases; in this specific case, secondary HLH is called "macrophage activation syndrome" (MAS).

The main element of both forms of HLH is the "cytokine storm" responsible for an uncontrolled and exaggerated immune response, potentially leading to organ dysfunction and death. Various cytotypes of innate and adaptive immune systems are involved in the cytokine storm. Macrophages release excessive cytokines with proinflammatory functions, such as interleukin (IL) -1, IL-6, IL-18, IL-33, and tumor necrosis factor (TNF), which cause serious tissue injury with potential organ dysfunction.

Activated macrophages are also responsible for excessive haemophagocytosis in bone marrow, leading to cytopenias common in patients affected by HLH [1]. NK cells in normal conditions can harm pathological cells mainly with a granzyme and perforin-mediated process; during cytokine storm, the large amount of IL-6 seems to inhibit this process, encouraging the pathogens' persistence and the development of further phlogosis.

Neutrophils injure tissues and amplify inflammation; furthermore, they release extracellular traps capable of promoting the creation of thrombi. T helper-1 (Th1) cells are the most involved during cytokine storm and release a large number of proinflammatory cytokines, such as interferon-γ, IL-6, and TNF; on the other hand, Th17 cells promote the recruitment of neutrophils, Th2 cells encourage the activation of eosinophils and basophils, Th9 cells activate mast cells. Like NK cells, the cytotoxic action of T cells CD8+ against pathogens is weakened, leading to inflammation maintenance. B cells seem not to be involved in the process of the cytokine storm. The diagnosis of HLH is based on the presence of five of the following eight HLH-2004 criteria: Fever (T >38,5 C°), splenomegaly, bicytopenia, hypertriglyceridemia and hypofibrinogenemia, hyperferritinemia, the sign of hemophagocytosis in bone marrow aspiration or biopsy, low or absent NK cell activity, increased levels of soluble CD25 [9].

In this last period, the novel Coronavirus infection, COVID-19, has established itself as another cause of Hemophagocytic lymphohistiocytosis. There are two different hypotheses of the pathogenesis of COVID-19-related cytokine storm: the first one identifies the viral infection as the trigger for the storm's development. This model is common to the other viruses mentioned above, such as EBV; on the other hand, the second one

suggests that the immunodeficiency induced by SARS-CoV-2, characterized by lymphopenia, and the consequent inability to remove the virus could lead to the development of a "second wave inflammation", similarly to primary HLH: in this scenario, IL-6 seems to play a critical role in the development of HLH, justifying the rationale of the therapeutic use of Tocilizumab, a monoclonal antibody against the IL-6 receptor [4].

The clinical case we have described is characterized by the onset of a hemophagocytic lymphohistiocytosis in a patient with a recent SARS-CoV-2 infection. During hospitalization, we observed spontaneous clinical and laboratory improvement in the absence of therapeutic measures of any kind, confirming the resolution of the picture through a six-month follow-up by hematochemical tests (Table 1). The fact that symptomatology started once the patient stopped the COVID-19 therapy with steroids suggests a possible correlation between HLH and the previous viral infection of the novel coronavirus. Furthermore, the persistence of the cytokine storm even after the recovery from COVID-19 could mean that HLH was not the result of the immunodeficiency and the consequent "second wave inflammation" provoked by SARS-CoV-2 infection.

Consequently, it seems to be reasonable to hypothesize that SARS-CoV-2 triggered the development of HLH similarly to other viral infections, such as EBV; nevertheless, it is not possible to exclude that HLH started during COVID-19 caused by the immunodeficiency related to the disease and continued even after the infective trigger disappeared. Steroids could have concealed the subacute progress of HLH, which was exacerbated after the interruption of the immunosuppressive therapy. The literature currently reports a few documented cases of COVID-19 patients and HLH with signs of hemophagocytosis in bone marrow aspiration or biopsy [3].

Conclusions

Our case report suggests some possible essential and novel issues concerning the correlation between infection of Covid 19 and the insurgence of HLH with a documented sign of hemophagocytosis in bone marrow aspiration. Moreover, we hypothesized that SARS-CoV-2 triggered the development of HLH similarly to other viral infections. Furthermore, our report proposes a viral etiology of sHLH even if it is impossible to exclude that HLH could have been caused by the immunodeficiency and the consequent cytokine storm and "second wave inflammation" induced by COVID-19. Sure of the fact that we have no firm evidence to determine what the exact pathogenesis of sHLH may have been in this case, we hope to have sparked a debate about the possible pathogenetic role that SARS-CoV-2 virus plays in hemophagocytic syndrome, but also about whether the onset of sHLH depends on the immunocompromising and subsequent cytokine storm that the viral infection induces, two sides of a coin that we cannot yet fully visualize.

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