Hemophagocytic syndrome after recovery from SARS-Cov-2 infection: a Case Report

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Case report

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Abstract

Background Hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory disease, whose diagnosis is based on the HLH-2004 criteria. In secondary forms of HLH (sHLH), the primary goal is treating the triggering factors such as SARS-CoV-2-19 infection. The link between the cytokine storm related to SARS-CoV-2-19infection and development of sHLH has already been reported since the onset of pandemic (1), but little is known about clinical manifestations of HLH which develop after patient's recovery from SARS-CoV-2-19 infection.

Case presentation A 56-year-old caucasian female was diagnosed with sHLH according to HLH-2004 criteria, after recovery from a mild symptomatic SARS-CoV-2-19 infection and received immunosuppressive treatment (high-dose steroids, IVIG, low dose Ruxolitinib and Etoposide. Antiviral (acyclovir), antibiotic (sulfamethoxazole / trimethoprim) and heparin prophylaxes were administered. Colchicine therapy was added considering the pericarditis. Improvement in patient symptoms and normalization of blood count as well as fibrinogen and ferritin values was observed.

Conclusion Our report suggests that HLH-like syndrome might be secondary to SARS CoV-2-19 infection, even after the patient completely recovered from the mildly symptomatic viral infection. In addition, we underline the treatment with low dose ruxolitinib plus etoposide as a potential choice for SARS-CoV-2-19 related HLH.

Introduction

Hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory disease. The diagnosis is based on the HLH-2004 criteria. (2)

The most recent HLH probability score (*Hscore*) may be a helpful diagnostic tool at the patient's initial presentation. (3) Moreover, hyperbilirubinemia, hepatomegaly, elevated LDH and D-dimer levels are common features of HLH, even if not included in HLH-2004 criteria. Mortality of HLH remains high in adults, around 70%, despite therapy. (1) In secondary forms of HLH (sHLH), the primary goal is treating the triggering factors such as SARS-CoV-2-19 infection. Of note, in COVID-19 (Coronavirus disease 2019) related sHLH, hemophagocytosis on bone marrow biopsy has not been reported so far. (4) Early high dose steroids and IVIG (1 gr/kg) for two days are considered the first line treatment of sHLH. The first cases of macrophage-activation syndrome (MAS) in association with COVID-19 infection were treated successfully with JAK inhibitors and IL-1 or IL-6 blockers. (5) (6)

Low dose ruxolitinib plus HLH-94 protocol has already been reported as a potential choice for sHLH. (7) Finally, in patients with severe active disease, a reduced dose of Etoposide (50-100 mg/mq once weekly) may be very effective. (2)

Case Presentation

In May 2020 a 56-year-old caucasian female was hospitalized for fever up to 40 °C, dry cough, ageusia and anosmia at Policlinico San Marco Hospital, Zingonia (Bergamo, Italy). Her past medical history was unremarkable. CT-scan revealed polyserositis: pericardial effusion, pleuro-parenchymal fibrosis of the lung bases associated with bilateral pleural effusion. During the hospitalization, three SARS-Cov-2 nasopharyngeal swabs were performed and each of them resulted negative. The patient was treated with empiric antibiotic therapy (ceftriaxone), without any improvement of her clinical conditions; multiple blood culture sets resulted negative and further antibiotic regimens (piperacillin-tazobactam, teicoplanin, meropenem, linezolid, levofloxacin) were unsuccessful. Viral infections (EBV, CMV, HIV, hepatotropic viruses and viruses transmitted by arthropods) were promptly ruled out, as well as atypical pneumonia by Mycoplasma or Chlamidya bacteria; autoimmune/autoinflammatory diseases were furtherly excluded. In the meantime, we observed lowering fibrinogen value, occurrence of cytopenias (anemia and thrombocytopenia), increasing value of ferritin

aspartate aminotransferase and triglycerides as well as splenomegaly and fever. Moreover, LDH and D-dimer were elevated. The individual risk of HLH the patient scored 269 points with >99% probability of having the syndrome (*HScore* see Table 1 and Table 2). *HScore* greater than 169 is 93% sensitive and 86% specific for hemophagocytic syndrome. Hemophagocytosis on bone marrow biopsy was not been reported. Considering that Bergamo and nearby cities have been the most affected area in Italy by COVID-19, SARS-Cov-2 IgGs were tested and found to be positive. The patient was diagnosed with hemophagocytic syndrome likely related to SARS-Cov-2 infection as a trigger factor and was treated with high-dose steroids and IVIG. Due to the persistence of fever and a further drop in platelets, haemoglobin and fibrinogen (which required platelet, blood and plasma transfusions), low-dose Ruxolitinib (5 mg bid) and Etoposide 100 mg/mq once weekly for eight weeks were added to the treatment, as well as antiviral (acyclovir), antibiotic (sulfamethoxazole / trimethoprim) and heparin prophylaxes, with subsequent improvement in patient symptoms, normalization of blood count and of fibrinogen and ferritin values (see figure 1 and 2), disappearance of fever and satisfactory remission of polyserositis. Colchicine therapy was added considering the pericarditis. After the end of the treatment, the patient has been followed on a regular basis and the disease is still in remission.

Discussion And Conclusion

The diagnosis of HLH can be very challenging. An increased awareness of this disease together with a rapid therapeutic approach can improve the prognosis. Nevertheless, HLH is still a severe and potentially fatal disease. Since other common causes of sHLH have been excluded, we suggest that HLH-like syndrome can develop at a distance from the viral infection, as a result of persistent inflammatory state. In addition, we underline the treatment with low dose ruxolitinib plus etoposide as a potential choice for COVID-19 related HLH.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of data and material

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors have no conflicts of interest to declare.

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Authors' contributions

FM and MMP analyzed and interpreted the patients’ data and drafted the manuscript; AD was a major contributor in writing the manuscript; all authors critically read and approved the final manuscript.

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Not applicable.

References

1. *Weathering the COVID-19 storm: Lessons from hematologic cytokine syndromes. .* **England JT, Abdulla A, Biggs CM, et al.** 2020, Vol. Blood Reviews, Vol. https//doi.org/10.1016/j.blre.2020.100707.
2. *HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis.* **Henet JI, Home A, Aricò M, et al.** s.l. : Pediatric Blood Cancer, 2007, Vol. 48;(2):124-131., 2007.
3. *Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. .* **Fardet L, Galicier L, Lambotte O, et al.** s.l. : Arthritis Rheumatology, 2014, 66(9):2613-2620., 2014.
4. *The unique characteristics of COVID-19 coagulopathy. .* **Iba T, Levy JH, Connors JM, et al.** s.l. : Critical care Vol. 24:360., 2020.
5. *Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. .* **Soy M, Atagunduz P, Atagunduz I, Sucak GT, et al.** 2020, Vol. Rheumatology International Vol. doi.org/10.1007/s00296-020-04636-y.
6. *Severe COVID-19, Another Piece in the Puzzle of the Hyperferritinemic Syndrome. An Immunomodulatory Perspectve to Alleviate the Storm. .* **. Ruscitti P, Beradicurti O, et al.** 2020, Vol. Frontiers in Immunology Vol. 1130.
7. *Low dose ruxolitinib plus HLH-94 protocol: a potential choice for secondary HLH. Seminar in Hematology, 2019, Vol. 9:28.* **Wang H, Gu J, Liang X, Mao X, Wang Z, et al.** Vol. Seminar in Hematology, 2019, Vol. 9:28.

Tables

Table 1 - HScore for reactive Hemophagocytic Syndrome.

Variable	Points		Patient's score
Known underlying immunosuppression HIV positive or receiving long-term immunosuppressive therapy (i.e., glucocorticoids, cyclosporine, azathioprine)	No	0	No
	Yes	+18	
Temperature, °F (°C)	<101.1 (<38.4)	0	
	101.1–102.9 (38.4-39.4)	+33	
	>102.9 (>39.4)	+49	39.5 °C
Organomegaly	No	0	
	Hepatomegaly or splenomegaly	+23	Splenomegaly
	Hepatomegaly and splenomegaly	+38	
Number of cytopenias Defined as hemoglobin ≤9.2 g/dL (≤5.71 mmol/L) and/or WBC ≤5,000/mm□ and/or platelets ≤110,000/mm□	1 lineage	0	
	2 lineages	+24	
	3 lineages	+34	Hb 7,7 g/dL, WBC 3700/mm□, platelets 27,000/mm□
Ferritin, ng/mL (or µg/L)	<2,000	0	
	2,000–6,000	+35	
	>6,000	+50	20,696 ng/mL
Triglyceride, mg/dL (mmol/L)	<132.7 (<1.5)	0	
	132.7-354 (1.5–4)	+44	
	>354 (>4)	+64	428 mg/dL
Fibrinogen, mg/dL (g/L)	>250 (>2.5)	0	
	≤250 (≤2.5)	+30	74 mg/dL
AST (Aspartate aminotransferase), U/L	<30	0	
	≥30	+19	59 U/L
Hemophagocytosis features on bone marrow aspirate	No	0	No
	Yes	+35	
Total			269 points (>99% probability of hemophagocytic syndrome)

Table 2 – HScore interpretation.

HScore	Probability of Hemophagocytic Syndrome
≤90	<1%
91-100	~1%
101-110	1-3%
111-120	3-5%
121-130	5-9%
131-140	9-16%
141-150	16-25%
151-160	25-40%
161-170	40-54%
171-180	54-70%
181-190	70-80%
191-200	80-88%
201-210	88-93%
211-220	93-96%
221-230	96-98%
231-240	98-99%
≥241	>99%

Figures

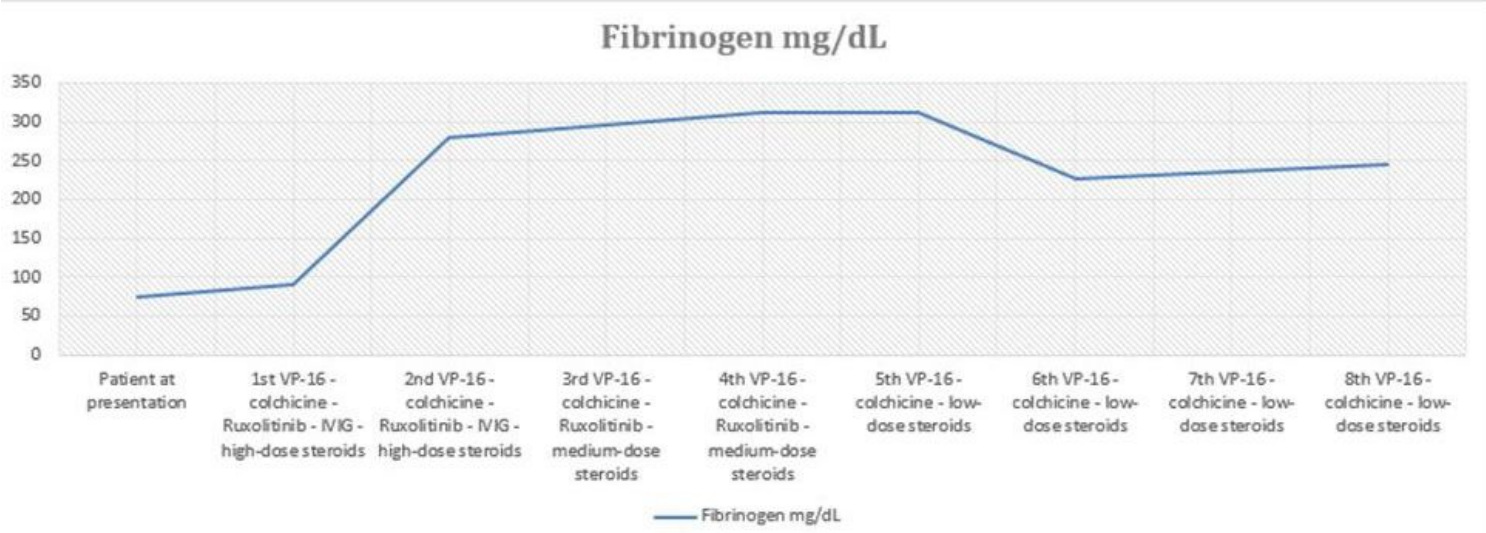

Figure 1

Patient's laboratory Fibrinogen response to treatment with: VP-16 100 mg/mq once a week; high-dose steroids: 10 mg/mq once a day; medium-dose steroids: 5 mg/mq once a day; low-dose steroids: 2.5 mg/mq once a day; Ruxolitinib: 10 mg once a day; Colchicine: 1 mg once a day. Fibrinogen normal range: 180-350 mg/dl.

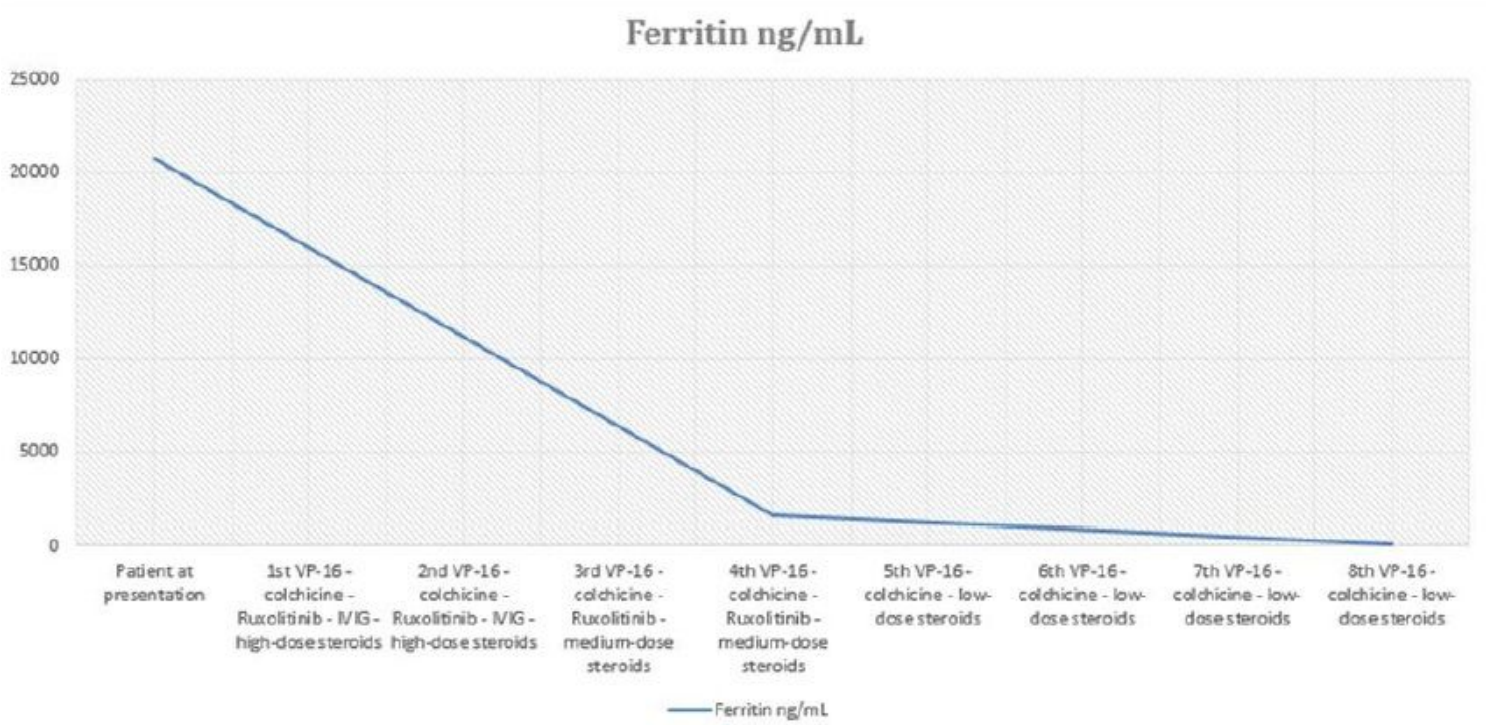

Figure 2

patient's laboratory ferritin response to treatment with: VP-16 100 mg/mq once a week; high-dose steroids: 10 mg/mq once a day; medium-dose steroids: 5 mg/mq once a day; low-dose steroids: 2.5 mg/mq once a day; Ruxolitinib: 10 mg once a day; colchicine: 1 mg once a day. Ferritin normal range: 7-130 mg/dl.