COVID-19 and Pembrolizumab-Induced Secondary Hemophagocytic Lymphohistiocytosis: a Case Report

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Abstract
Our case highlights SARS-CoV-2 and pembrolizumab as trigger of secondary hemophagocytic lymphohistiocytosis. Although it is a rare complication, it must be suspected in order to start specific treatment. In this context, intravenous immunoglobulins could be a therapeutic option.

Keywords Hemophagocytic lymphohistiocytosis · Hemophagocytic syndrome · Pembrolizumab · COVID-19 · SARS-CoV-2

Introduction
The 2019 novel coronavirus disease (COVID-19), caused by SARS-CoV-2 infection, still remains a global health problem. Approximately, 5% of patients suffer from the COVID-19 severe form consistent in the development of an immune-mediated acute respiratory distress syndrome (ARDS) [1]. A dysregulated immune response and the so-called cytokine storm syndrome (CSS) had been implied in the pathogenesis. Immunological profile of severe COVID-19 patients showed increase in proinflammatory cytokines as IL6, IL10, TNF-α, IL8, and IL10 and decrease of T CD4 and T CD8 lymphocytes [2]. This inflammatory profile, together with clinical characteristics of severe COVID-19 as fever, acute phase reactants, and ferritin elevation, resembled in part to hemophagocytic lymphohistiocytosis (HLH), where cytokine storm also has an important role. HLH is an hyperinflammatory CSS mainly mediated by aberrant T cell response. HLH may be primary due to specific genetic mutations or secondary (sHLH) to infections, neoplasm, or autoimmune disorders [3]. Viral infection is the main trigger for sHLH in adults, and some cases of sHLH related to COVID-19 have been described [4]. Several therapeutic alternatives had been proposed since the beginning of the pandemic caused by COVID-19, among them are checkpoint inhibitors directed against PD1/PDL1 as they may mitigate lymphocyte exhaustion and defective activation of T lymphocyte caused by SARS-CoV-2 infection [2]. We present the case of a patient under treatment with anti-PD1 antibodies infected by SARS-CoV-2 who develop sHLH and was successfully treated with intravenous immunoglobulins (IVIG).

Case Report
A 76-year-old man undergoing treatment with anti-PD1 antibody (pembrolizumab) for lung adenocarcinoma consulted in the Emergency Department for fever and 1 week of dyspnea. Physical examination revealed peripheral oxygen saturation < 90%, requiring supplemental oxygen. No infiltrates were found on the chest X-ray, despite a positive polymerase chain reaction (PCR) for SARS-CoV-2 in nasopharyngeal swab. Initial blood test results are shown in Table 1. During admission, he received treatment with hydroxychloroquine and respiratory support for 10 days, being discharged upon resolution of fever and respiratory symptoms. Two weeks later, he returned to the hospital, due to high unremittent daily fever up to 39°. No clear etiology was evident in the anamnesis, and the physical examination was unremarkable, excepting the fever. Broad-spectrum antibiotics were initiated (meropenem, linezolid, and trimethoprim-sulfamethoxazole). Blood cultures were negative on several occasions; cytomegalovirus and Epstein-Barr virus viral loads were undetectable; serologies for syphilis, HIV, hepatitis B, hepatitis C, Mycoplasma
pneumoniae, Coxiella burnetti, and Parvovirus B19 were negative; and Interferon Gamma Release Assay (IGRA) tested negative. However, SARS-CoV-2 PCR remained positive in the nasopharyngeal swab. Despite antibiotic treatment, daily fever persisted, and clinical and analytical parameters worsened presenting pancytopenia, organomegaly, and elevation of ferritin and cytokine profile (Table 1). A positron emission tomography performed was unremarkable. At that point, calculated Hscore score was 211, conferred a 93.65% probability of his clinical condition being caused by hemophagocytic lymphohistiocytosis [5]. Bone marrow examination was not obtained. High-dose intravenous immunoglobulins (IVIG) (1 g/Kg × 2 days) were started, with fever disappearance, hemodynamic improvement, and attenuation of acute phase reactants (Table 1). The patient improved and was discharged without presenting recurrence in the follow-up.

### Discussion

HLH and cytokine storm syndrome related to severe COVID-19 (COVID-19-CSS) had some characteristics in common, including the presence of hemophagocytosis [4, 6]. However, COVID-19-CSS has predominant pulmonary affection, and trends to have less ferritin elevation and organomegaly and pancytopenia are not frequent [7, 8] (Table 2).

Many articles published so far have tried to answer the question of the prevalence of HLH in COVID-19 disease and if it is linked to COVID-19-CSS. Hscore was initially design for evaluation of secondary HLH [5] and had not performed well as a risk score tool in COVID-19 [9]. The presence of hemophagocytosis in different tissue samples was not specific of HLH in COVID-19 autopsies [4]. However, Hscore was more elevated in patients diagnosed of HLH in the context of COVID-19 than in the rest of critical COVID-19 patients [4, 10]. Prevalence of HLH in COVID-19 varies from 2 to 17% among series [10, 11]. Nevertheless, several case reports and case series had reported SARS-CoV-2 as a trigger of secondary HLH [12]. What made us lean towards the diagnosis of HLH in our patient was the presence of severe pancytopenia and organomegaly. Also, pre- and post-IVIG sera were evaluated retrospectively for a set of cytokines typically associated with COVID-19-CSS (Table 1). Elevation of several pro-inflammatory cytokine and factors was evidenced.
not fully resembling the phenotype described in COVID-19-
CSS [13]. In this line, IVIG treatment induced a tempering of
cytokines levels measured before and after its infusion.

One interesting point is the fact that this patient was under
treatment with pembrolizumab, an anti-PD1 antibody. PD1/
PDL1 immune checkpoint inhibitors, widely used in cancer
therapy, had been proposed as treatment of COVID-19 be-
cause of their potential to revert the lymphocyte exhaustion
and defective activation of T cells promoted by SARS-CoV-2
[14]. Treatment with PD-1 checkpoint inhibitors induce an
immune-modulated state characterized by a non-specific im-
mune activation, mainly due to the blocking of PD-1 in T
lymphocytes, especially CD8+ [15]. Anti-PD-1 treatment dur-
ing COVID-19 infection has been reported safely in oncologic
patients [16, 17]. However, an association between immune
checkpoint inhibitors treatment and sHLH had been well de-
scribed in literature [18]. This set the hypothesis that treatment
with pembrolizumab in this patient had probably contributed
to the development of sHLH in concurrence with SARS-CoV-
2 infection. Secondary hemophagocytic lymphohistiocytosis
may appear in the context of COVID-19 infection, even more
if the patient is under treatment with anti PD1/PDL1 check-
point inhibitors; clinicians must be awarded in order to initiate
specific treatment.

Code Availability  Not applicable.

Author Contribution  All authors have contributed in the redaction, revis-
ion, and correction of the manuscript.

Data availability  Not applicable, as is a case study report.

Declarations

Ethics Approval  The Ethics Committee of the Hospital Universitario La
Paz waived the need for ethics approval for this non-interventional study.

Consent to Participate  Not applicable, as there was no intervention.
Patient informed consent was obtained for the publication of the manuscript.

Competing Interests  The authors declare no competing interests.

References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and
risk factors for mortality of adult inpatients with COVID-19 in
Wuhan, China: a retrospective cohort study. Lancet. 2020;395:
1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.

2. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in
COVID-19: the current evidence and treatment strategies. Front
Immunol. 2020;11:1–13. https://doi.org/10.3389/fimmu.2020.
01708.

3. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashia
MA, Bosch X. Adult haemophagocytic syndrome. Lancet.
2014;383:1503–16. https://doi.org/10.1016/S0140-6736(13)
61048-X.

4. Prituliski A, Kritselis M, Shevtsov A, Yambayev I, Vadamudi C,
Zhao Q, et al. SARS-CoV-2 infection–associated hemophagocytic
lymphohistiocytosis an autopsy series with clinical and laboratory
correlation. Am J Clin Pathol. 2020;154:466–74. https://doi.org/10.
1093/ajcp/AQAA124.

5. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan
D, et al. Development and validation of the hscore, a score for the
diagnosis of reactive hemophagocytic syndrome. Arthritis
Rheumatol. 2014;66:2613–20. https://doi.org/10.1002/art.36909.

6. Deblaquís A, Harzallah I, Moootien JY, Poidevin A, Labro G, Mejri
A, et al. Haemophagocytosis in bone marrow aspirates in patients
with COVID-19. Br J Haematol. 2020;190:e70–3. https://doi.org/10.
1111/bjh.16860.

7. Hakim NN, Chi J, Olazagasti C, Liu JM. Secondary
hemophagocytic lymphohistiocytosis versus cytokine release syn-
drome in severe COVID-19 patients. Exp Biol Med. 2020;246:1–5.
https://doi.org/10.1177/1535370220926043.

8. Lorenz G, Moog P, Bachmann Q, La Rosée P, Schneider H,
Schlegl M, et al. Title: Cytokine release syndrome is not usually
causative by secondary hemophagocytic lymphohistiocytosis in a
cohort of 19 critically ill COVID-19 patients. Sci Rep. 2020;10:1–11.
https://doi.org/10.1038/s41598-020-75260-w.

9. Clark KEN, Nevin WD, Mahungu T, Lachmann H, Singh A.
Assessment of the hemophagocytic lymphohistiocytosis HScore
in patients with coronavirus disease 2019. Clin Infect Dis. 2020.
https://doi.org/10.1093/cid/ciaa1463.

10. Yang K, Xing M, Jiang L, Cai Y, Yang L, Xie N, et al. Infection-
associated hemophagocytic syndrome in critically ill patients
with COVID-19. Curr Med Sci. 2021;41:39–45. https://doi.org/10.1007/
s11596-021-2315-4.

11. Huessu T, Bouchez C, Salviat F, Foulon S, Albiges L, Bayle A, et al.
Secondary haemophagocytic lymphohistiocytosis is a rare occur-
rence amongst cancer patients with COVID-19. Br J Haematol.
2021;192:e87–90. https://doi.org/10.1111/bjh.17275.

12. Retamozo S, Brito-Zerón P, Sísó-Almirall A, Flores-Chávez A,
Soto-Cárdenas MJ, Ramos-Casals M. Haemophagocytic syndrome
and COVID-19. Clin Rheumatol. 2021;40:1233–44. https://doi.
org/10.1007/s10067-020-05569-4.

13. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation
of immune response in patients with coronavirus 2019 (COVID-19)
in Wuhan, China. 2019;2020:4–10. https://doi.org/10.1038/s41304-
cia248.
14. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol. 2020;11. https://doi.org/10.3389/fimmu.2020.00827.

15. Kamphorst AO, Pillai RN, Yang S, Nasti TH, Akondy RS, Wieland A, et al. Proliferation of PD-1+ CD8 T cells in peripheral blood after PD-1-targeted therapy in lung cancer patients. Proc Natl Acad Sci. 2017;114:4993–8. https://doi.org/10.1073/pnas.1705327114.

16. Pala L, Conforti F, Saponara M, De Pas T, Giugliano F, Omodeo Salè E, et al. Data of Italian Cancer Centers from two regions with high incidence of SARS CoV-2 infection provide evidence for the successful management of patients with locally advanced and metastatic melanoma treated with immunotherapy in the era of COVID-19. Semin Oncol. 2020;47:302–4. https://doi.org/10.1053/j.seminoncol.2020.07.010.

17. Bersanelli M, Zielli T, Perrone F, Casartelli C, Pratico F, Rapacchi E, et al. Clinical impact of COVID-19 in a single-center cohort of a prospective study in cancer patients receiving immunotherapy. Immunotherapy. 2020;12:1139–48. https://doi.org/10.2217/imt-2020-0211.

18. Noseda R, Bertoli R, Müller L, Ceschi A. Haemophagocytic lymphohistiocytosis in patients treated with immune checkpoint inhibitors: analysis of WHO global database of individual case safety reports. J Immunother Cancer. 2019;7:1–6. https://doi.org/10.1186/s40425-019-0598-9.

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