Be-careful! Behind the storm of severe COVID-19, could be hidden macrophage activation syndrome. A case report with excellent outcome.

Rafaela Silva Guimarães Gonçalves (rafa_sgg@hotmail.com)
Hospital da Clinicas da Universidade Federal de Pernambuco

André da Costa Victor
Laboratório Edmar Victor

Ana Carolina Oliveira Cavalcanti Tavare
Hospital Maria Lucinda

Angela Luzia Branco Pinto Duarte
Hospital da Clinicas da Universidade Federal de Pernambuco

Case Report

Keywords: COVID-19, MAS, IVIG, methylprednisolone

DOI: https://doi.org/10.21203/rs.3.rs-47499/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

In severe cases of COVID-19, it is important to note that some laboratory signs may alert to the presence of underlying macrophage activation syndrome (MAS), and we ratify that the classic signs of primary MAS are often not present. Here we show a case report of COVID-19 complicated by MAS treated with high doses of methylprednisolone and intravenous Immunoglobulin, with excellent clinical outcome, avoiding orotracheal intubation indeed. The interpretation of laboratory signs leads to early diagnosis and the introduction of effective therapy.

Keypoints

- MAS in COVID-19 could be present without the classic signs of primary MAS, such as
- Reduced of ESR despite the context of inflammation and anemia, is an extremely important clue of MAS
- Early diagnosis is crucial for a favorable outcome

Introduction

The COVID-19 pandemic caused by infection with SARS-CoV-2, has morbidity and mortality associated with excessive inflammation. Higher levels of inflammatory markers in blood (including C-reactive protein (CRP), ferritin, and D-dimer), an increased neutrophil-to-lymphocyte ratio and increased serum levels of several inflammatory cytokines and chemokines have been associated with disease severity and death.[1-3]

A macrophage activation syndrome (MAS) has been described during infection with highly pathogenic coronaviruses, such as SARS-CoV and MERS-CoV, in 20% of patients who progressed to fatal SARS. In the postmortem evaluation of these patients, extensive cellular infiltration dominated by macrophages was found in the lungs.[3] The serum of patients with SARS-CoV-2 infection has an increased level of cytokines, such as IFN-γ, IFN-α, IL-6, IL-1β, IL-18, IL-12, TGFβ, IL-33, TNF-α and chemokines like CCL2, CCL5, CCL3, CXCL10, CXCL9 and CXCL8. This cytokine storm causes multiple organ failure, responsible for the death of these patients.[4-6]

A MAS is part of hyperferritenic syndromes (HS), characterized by high serum ferritin and sustained hyper-inflammation due to a life-threatening cytokine storm that eventually leads to multiple organ failure. A severe form of COVID-19 shares several clinical and laboratory features with entities included in the definition of HS.[6-8]

Our objective with this case report was to point out that MAS is a real and serious complication in COVID-19, which must be diagnosed early, once immediate and aggressive treatment can contribute to patient’s survival.
Case Report

On May 4, 2020, a 73-year-old man was admitted to the Jayme da Fonte Hospital with a complicated clinical picture of COVID-19 (on the 10th day of the disease's evolution). Patient had had a sore throat since April 25 and reported light fever two days after during for 9 days with the highest temperature at 38°C. He was given oseltamivir and ivermectin by a local clinic empirically at the first day, since already had a confirmed case in the family. On April 27 besides any improvement were seen and was presenting hypoxemia (SatO2: 91%), he was to the emergency and a computed tomography (CT) scan was done. There were two small peripheral amorphous opacities with ground-glass density. At the time azithromycin and hydroxychloroquine were added to therapeutic approach. Oropharyngeal swab was positive for SARS-CoV-2 by RT-PCR assay. He had history of hypertension, diabetes, chronic kidney disease and gout.

On admission he was febrile 37,8°C, with blood pressure 130/80 mmHg, pulse 96 beats per minute, respiratory rate 25 breaths per minute, and oxygen saturation oscillating between 88 to 94% when breathing ambient air and prone position. On auscultation both lungs were rude.

CT was repeated and worsened pneumonia, with presence of multiple ground-glass opacities dispersed in practically all predominantly peripheral pulmonary lobes, located mainly in the posterior aspect of lower lobes, associated with foci of consolidation of the pulmonary parenchyma, and in addition to thickening of the interlobular septa affecting in that moment about 50% of both lung (figure 1A). Laboratory results (Table 1) reflected a significant lymphocytopenia (600/mm³), anemia 10.8 g/dL and mild thrombocytopenia at 109,000/mm³. His inflammatory markers were elevated, with increased high-sensitive C-reactive protein (hsCRP) 159mg/L, a mild high erythrocyte sedimentation rate (ESR) 48 (0–15) mm/h, and increased D-dimer 2.88 µ/ml. The patient had worsening renal function with creatinine 2.23 mg/dL, but liver function normal.

On the same day of admission, supportive care and empirical heparin in full dose, methylprednisolone 80mg and Ceftriaxone were given, with close monitoring of clinical status. On May 6, drop in hemoglobin was noted and erythrocyte sedimentation rate did not increase proportionally, ferritin 1136 ng/ml and a myelogram had done. The myelogram had shown hemophagocytic activity in the erythroid, myeloid and platelet series (figure 2).

On May 7, the patient developed shortness of breath and his oxygen saturation decreased to 88% when breathing ambient air, and 92-94% on 10 liters of oxygen by nasal catheter. A CT was repeated and showed progressing infiltrations bilaterally reaching about 80% (figure 1A).

The patient was admitted to the ICU, Ceftriaxone was changing by Tazocin and Targocid, 2g/kg IVIg was started at 400mg/kg for 5 days, and metilprednisolone was increased for 1000mg on the first day, 250mg on the second and third day, and then maintained with 80mg/day completing ten days. In the first day of infusion he reported malaise, which was solved by reducing the infusion flow. After the last IVIg infusion CT has repeated and already showing improved (figure 1B).
Over the next few days, his clinical status gradually improved, and supplemental oxygen was discontinued on May 14, and his oxygen saturation level returned to 97–98% on when breathing ambient air. The result of laboratory tests on May 14 showed recovered lymphocyte count to 1190/mm$^3$, Hb 11 g/dL, creatinine 1.63 mg/dL and hsCRP 2.39 mg/L.

**Discussion**

It has been recognized that COVID-19 illness exhibits three grades of increasing severity, which correspond with distinct clinical findings, response to therapy, and clinical outcome: stage 1 (mild) early infeccion, stage II (moderate)—pulmonary involvement (IIa) without hypoxia and (IIb) with hypoxia, and stage III (severe)—systemic hyperinflammation.[9] In this last phase the markers of systemic inflammation seem to be elevated such as IL-2, IL-6, IL-7, granulocyte colony-stimulating factor, macrophage inflammatory protein 1-a, TNF-α, CRP, ferritin, and D-dimer characterizing patients with more severe disease.[3, 4, 9]

Clinical and laboratory parameters in the COVID-19 are similar with MAS. Laboratory parameters including highly elevated CRP and hyperferritinemia, the latter of which may play a complex role in disease, are key to the diagnosis of MAS and are elevated in many severe COVID-19 pneumonia cases. Other features including coagulopathy and abnormal liver function may be evident suggesting that a subgroup of COVID-19 pneumonia cases also have MAS, without having organomegaly. In common with the disseminated intravascular coagulation (DIC) associated with MAS, there is evidence of D-dimer level elevation in COVID-19 pneumonia which might represent an extension of this novel virally induced hyper-inflammatory pulmonary immunopathology to the adjacent microcirculation with extensive secondary fibrinolytic activation.[6]

“MAS like-syndrome” can occur in patients at this advanced stage of the disease, thus all patients with severe COVID-19 they should be screened for MAS with laboratory tests should be interpreted looking for tendencies to increase ferritin, decreased platelets, and undoubtedly an important clue to MAS is the reduction of erythrocyte sedimentation rate in the face of acute anemia and infection. The interpretation of laboratory signs is essential to alert the possibility of MAS associated.[10]

The HScore [11] can be applied to identify the subgroup of patients most likely to have MAS for whom immunosuppression could be instituted and thus improve mortality. However, it is important to highlight that for the realization and validation of this score, most of the infections included were due to bacteria or mycobacteria, and therefore it may not be appropriate to apply this score to COVID-19 infections.

In a retrospective study of fatal cases of COVID-19 in two hospitals in Wuhan, the majority of patients died from multiple organ failure. Of the 85 patients, 58 (68.2%) had one or more comorbidities. The majority were men (72.9%) aged ≥ 65 years (61.2%). The most common cause of death in 81/85 patients was respiratory failure (46, 91%), followed by septic shock (19, 75%), multiple organ failure (13, 16.05%) and cardiac arrest (7, 8.64%). Chest computed tomography was performed on 80 patients, 76.3% having
multiple ground-glass opacities. Among the laboratory characteristics, the most frequent were leukocytosis, neutrophilia, thrombocytopenia, eosinopenia, in addition to increased CRP, D-dimer, fibrinogen and DHL. It is possible that some patient developed “MAS like-syndrome”, but this diagnosis was not mentioned, pointing out that 33% of the patients received intravenous infusions of immunoglobulin.[12]

Therefore, the overlapping cytokine profiles between severe ARDS and MAS may limit the utility of cytokine profiling in the differentiation between both conditions and many of the laboratory changes reported in COVID-19 could predominantly reflect ARDS. COVID-19 severe pneumonia may represent a novel viral MAS-like immunopathology, where hyper-inflammation may be key to virus control in the face of disabled type-1 interferon responses. Furthermore, the recognition of MAS is problematic in COVID-19 pneumonia cases with the severe inflammation emanating from the pulmonary compartment mimicking MAS, but the lack of other classical systemic clinical features making MAS presentation atypical and diagnosis more difficult.[6]

For the treatment of MAS, we have as therapeutic options oral or pulse steroids, intravenous immunoglobulin, selective blocking of IL-6 and IL-1β, in addition to JAK inhibitors.[5, 8, 10]

In the case report of this patient, as he is elderly, with multiple comorbidities that could predispose the possibility of secondary bacterial infection, we opted in addition to coverage with antibiotics, started IVlg and corticosteroids. This strategy has already by Hutchinson et al [13] that suggested immediate use of IVlg 2g/kg associated with intravenous methylprednisolone (1g from 3 to 5 days). As our patient is diabetic, we chose to make 1g of methylprednisolone only on the first day, and 250 mg on the next two days, always reevaluating the need or not to increase the dose through the results of laboratory tests and clinical signs, and it was not necessary increase as we could demonstrate.

IVlg is a pooled preparation of normal immunoglobulin IgG obtained from several thousand healthy donors [14] and has an important role in the treatment of MAS and serves to reduce inflammation by several mechanisms, including reducing complement activation and cytokine inhibition.[15, 16] It may also have the additional benefit of counteracting some of the immune deficiency brought about by other drugs and the disease state. However, there are potential side effects of IVlg,[17] and as we have shown in the clinical case, the flow of the infusion should be done with caution, starting with 25ml/h and gradually increasing according to the patient’s tolerability. IVlg has been also reported as a treatment key for severe cases of COVID-19 in previous studies.

Corticosteroids are a fundamental part of the treatment of MAS. In rheumatologic practice, there is a tendency to give pulsed intravenous methylprednisolone at the outset [18]. Meanwhile, in adult haematology practice, dexamethasone is used.[19] In the treatment of severe pneumonia, whether by COVID-19 or not, the use of corticosteroids is well established. However, whether with methylprednisolone,[20, 21] or with dexamethasone,[22] the doses for adjuvant treatment in severe viral pneumonia are lower, since they respond well to low doses of corticosteroids. The problem here is to draw attention to cases in
which macrophage inflammation presents itself systematically as MAS, and in these cases, low doses of corticosteroids will not be enough.

**Conclusion**

It is necessary to keep in mind that COVID-19 is a hyperferritinemic syndrome and that it can degenerate into MAS without the classic signs of primary MAS, such as organomegalies. Observing the rate of erythrocyte sedimentation, for example, if reduced despite the context of inflammation and anemia, is an extremely important clue of MAS.

The assessment of each patient individually and the interpretation of clinical and laboratory signs are the key to for early and correct diagnosis, which implies an effective therapy with possibilities of full recovery.

**Declarations**

**Correspondence to** Dr Rafaela Silva Guimarães Gonçalves, Hospital das Clinicas de da Universidade Federal de Pernambuco, Recife 50670-901, Brazil; rafa_sgg@hotmail.com

**Acknowledgements** We thank our patient.

**Contributors** All contributors meet criteria for authorship.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** The patient consented to publish this case.

**References**

1. Ruan Q, Yang K, Wang W, Jiang L, Song J: **Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China.** *Intensive Care Med* 2020, 46(5):846-848.

2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X *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(10229):1054-1062.

3. Merad M, Martin JC: **Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages.** *Nat Rev Immunol* 2020, 20(6):355-362.

4. Renu K, Prasanna PL, Valsala Gopalakrishnan A: **Coronaviruses pathogenesis, comorbidities and multi-organ damage - A review.** *Life Sci* 2020, 255:117839.

5. Felsenstein S, Herbert JA, McNamara PS, Hedrich CM: **COVID-19: Immunology and treatment options.** *Clin Immunol* 2020, 215:108448.
6. McGonagle D, Sharif K, O'Regan A, Bridgewood C: The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmun Rev* 2020, 19(6):102537.

7. Shoenfeld Y: Corona (COVID-19) time musings: Our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning. *Autoimmun Rev* 2020, 19(6):102538.

8. Colafrancesco S, Alessandri C, Conti F, Priori R: COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome? *Autoimmun Rev* 2020, 19(7):102573.

9. Siddiqi HK, Mehra MR: COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. *J Heart Lung Transplant* 2020, 39(5):405-407.

10. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, Hlh Across Speciality Collaboration UK: COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020, 395(10229):1033-1034.

11. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piacentini M, Ippolito G, Melino G: COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 2020, 27(5):1451-1454.

12. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, Wang X, Hu C, Ping R, Hu P et al: Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan. A Retrospective Observational Study. *Am J Respir Crit Care Med* 2020, 201(11):1372-1379.

13. Hutchinson M, Tattersall RS, Manson JJ: Haemophagocytic lymphohistiocytosis- an underrecognized hyperinflammatory syndrome. *Rheumatology (Oxford)* 2019, 58(Suppl 6):vi23-vi30.

14. Galeotti C, Kaveri SV, Bayry J: IVIG-mediated effector functions in autoimmune and inflammatory diseases. *Int Immunol* 2017, 29(11):491-498.

15. La Rosee P: Treatment of hemophagocytic lymphohistiocytosis in adults. *Hematology Am Soc Hematol Educ Program* 2015, 2015:190-196.

16. Lutz HU, Stammler P, Bianchi V, Trueb RM, Hunziker T, Burger R, Jelezarova E, Spath PJ: Intravenously applied IgG stimulates complement attenuation in a complement-dependent autoimmune disease at the amplifying C3 convertase level. *Blood* 2004, 103(2):465-472.

17. Katz U, Achiron A, Sherer Y, Shoenfeld Y: Safety of intravenous immunoglobulin (IVIG) therapy. *Autoimmun Rev* 2007, 6(4):257-259.

18. Carter SJ, Tattersall RS, Ramanan AV: Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology (Oxford)* 2019, 58(1):5-17.

19. George MR: Hemophagocytic lymphohistiocytosis: review of etiologies and management. *J Blood Med* 2014, 5:69-86.

20. Shang L, Zhao J, Hu Y, Du R, Cao B: On the use of corticosteroids for 2019-nCoV pneumonia. *Lancet* 2020, 395(10225):683-684.

21. Zha L, Li S, Pan L, Tefsen B, Li Y, French N, Chen L, Yang G, Villanueva EV: Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). *Med J Aust* 2020, 212(9):416-420.
22. Villar J, Ferrando C, Martinez D, Ambros A, Munoz T, Soler JA, Aguilar G, Alba F, Gonzalez-Higueras E, Conesa LA et al: Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med* 2020, **8**(3):267-276.

### Tables

#### Table 1. Laboratory Tests

| Measures (Normal ranges) | Illness Days |
|--------------------------|--------------|
|                         | 5th | 1st Hosp | 10th | 11th | 12th | 1st ICU | 13th | 14th | 18th | 20th | 26th |
| WBC (109/L) 4.5-11       |     |         |      |      |      |          |      |      |      |      |      |
|                         | 4.8 | 7.5     | 11.5 | 9.9  | 8.7  | 9.8      | 7.8  | 8.2  | 10.4 |      |      |
| RBC (1012/L) 4.5-5.9     |     |         |      |      |      |          |      |      |      |      |      |
|                         | 4.53| 3.48    | 3.63 | 3.47 | 3.44 | 3.8      | 3.34 | 3.6  | 3.31 |      |      |
| Hb (g/dL) 13.5-17.5      |     |         |      |      |      |          |      |      |      |      |      |
|                         | 13.5| 10.8    | 11.2 | 10.8 | 10.5 | 11.5     | 10.4 | 11   | 10.4 |      |      |
| PLT (109/L) 150-450      |     |         |      |      |      |          |      |      |      |      |      |
|                         | 163 | 109     | 131  | 160  | 172  | 205      | 224  | 252  | 292  |      |      |
| NEUT (109/L) 1.6-7.7     |     |         |      |      |      |          |      |      |      |      |      |
|                         | 2.6 | 6.3     | 9.6  | 8.81 | 7.48 | 8.42     | 6.2  | 6.3  | 9.15 |      |      |
| LYM (109/L) 1.1-3.9      |     |         |      |      |      |          |      |      |      |      |      |
|                         | 1.6 | 0.6     | 1.38 | 0.59 | 0.78 | 0.68     | 0.99 | 1.19 | 1.0  |      |      |
| ESR (mm/h) <20          |     |         |      |      |      |          |      |      |      |      |      |
|                         | NR  | 48      | 69   | 36   | NR   | NR       | NR   | NR   | 35   | NR   |      |
| hsCRP (mg/L) 0-3         |     |         |      |      |      |          |      |      |      |      |      |
|                         | 11.94| 159.1 | 187.8| 124.7| 92.7 | 80.4     | 14.3 | 2.39 | 3.5  |      |      |
| SF (ng/ml) 22-320        |     |         |      |      |      |          |      |      |      |      |      |
|                         | 426 | NR      | 1136 | 1300 | 876  | 869      | 585  | NR   | NR   |      |      |
| Tn (ng/L) 0-14           |     |         |      |      |      |          |      |      |      |      |      |
|                         | NR  | NR      | 14   | 10   | NR   | NR       | NR   | NR   | NR   |      |      |
| LDH (U/L) 120-246       |     |         |      |      |      |          |      |      |      |      |      |
|                         | 180 | 386     | NR   | NR   | 360  | 375      | NR   | 256  | 190  |      |      |
| ALB (g/dL) 3.4-4.8       |     |         |      |      |      |          |      |      |      |      |      |
|                         | 4.1 | 2.8     | NR   | NR   | 2.4  | NR       | NR   | NR   | NR   |      |      |
| TBIL (mg/dL) 0.3-1.2     |     |         |      |      |      |          |      |      |      |      |      |
|                         | NR  | NR      | 0.23 | NR   | 0.3  | 0.4      | NR   | NR   | NR   |      |      |
| ALT (U/L) 6-41          |     |         |      |      |      |          |      |      |      |      |      |
|                         | 24  | 17      | 16   | NR   | 19   | 29       | NR   | 25   | NR   |      |      |
| AST (U/L) 15-37         |     |         |      |      |      |          |      |      |      |      |      |
|                         | 34  | 35      | 38   | NR   | 42   | 52       | NR   | 24   | NR   |      |      |
| γ-GT (U/L) 15-85        |     |         |      |      |      |          |      |      |      |      |      |
|                         | NR  | NR      | 141  | NR   | 179  | NR       | NR   | NR   | NR   |      |      |
| CRE (mg/dL) 0.5-1.3     |     |         |      |      |      |          |      |      |      |      |      |
|                         | 0.9 | 2.23    | 1.99 | 1.64 | 1.8  | 1.69     | 1.66 | 1.63 | 1.44 |      |      |
| Ur (mg/dL) 15-50        |     |         |      |      |      |          |      |      |      |      |      |
|                         | 40  | 60      | 61   | 62   | 58   | 49       | 80   | 80   | 82   |      |      |
| CK (U/L) 39-308         |     |         |      |      |      |          |      |      |      |      |      |
|                         | 55  | NR      | 115  | NR   | NR   | NR       | NR   | NR   | 43   |      |      |
| D-Dimer (μg/mL) 0-0.5   |     |         |      |      |      |          |      |      |      |      |      |
|                         | 2   | 2.88    | >20  | 2.61 | NR   | 1.59     | 1.81 | 1.35 | 0.97 |      |      |
| FIB (mg/dL) 200-400     |     |         |      |      |      |          |      |      |      |      |      |
|                         | 347 | NR      | 616  | 647  | NR   | NR       | NR   | NR   | NR   |      |      |

**Abbreviations:** WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; PLT, platelet count; NEUT, absolute neutrophil count; LYM, absolute lymphocyte count; ESR, erythrocyte sedimentation rate; NR, Not Realized; hsCRP, hypersensitive C-reactive protein; SF, serum ferritin; Tn, troponin; LDH, lactate dehydrogenase; ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ- glutamyltransferase; CRE, creatinine; Ur, Urea; CK, creatine kinase; FIB, fibrinogen.
Figures
Figure 1

Chest computed tomography scan of patient: (A) 1st day of admission in the Hospital and three days after, (B) before and after infusion intravenous immunoglobulin with days of illness, (C) on day after the last day of infusion intravenous immunoglobulin and eight days after.
Figure 2

Mielogram. (A) and (B) both images show histiocytes phagocytizing red blood cells; (C) Image shows a histiocyte phagocytizing a leukocyte, however the leukocyte degeneration does not allow what kind of leukocyte is it; and (D) the image shows histiocyte in phagocytic activity with the presence of two polymorphonuclear cells (red arrows) and one red cell (blue arrow).