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Letter to the Editor

Severe Autoimmune Hemolytic Anemia in COVID-19 İnfection, Safely Treated with Steroids

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To the editor.

In December 2019, a novel pneumonia syndrome was identified in patients clustered around the Seafood Market in Wuhan, China.[1] This novel coronavirus was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Infection with SARS-CoV-2 leads to the syndrome of Coronavirus Disease 2019 (COVID-19). The clinical spectrum of symptomatic Covid-19 cases ranges from mild to critically ill.[1] While the majority of patients have mild symptoms without pneumonia or mild pneumonia, 14% of patients present with severe pneumonia, 5% of patients develop a critical disease with acute respiratory distress syndrome (ARDS), cardiac injury, renal injury, or multiorgan failure.[1] Autoimmune disorders including immune thrombocytopenia, Guillain-Barré and antiphospholipid syndrome have been recognized in the context of Covid-19 infection.[2-4]

Autoimmune hemolytic anemia (AIHA) is a rare autoimmune disorder characterized by autoantibodies that react with self red blood cells and result in their destruction. Warm agglutinin disease accounts for the majority of AIHA and is generally mediated by IgG antibodies to the Rh system of erythrocytes. Pathogens associated with warm agglutinin disease include human immunodeficiency virus (HIV), hepatitis C virus (HCV), and infectious mononucleosis. Association of AIHA with COVID-19 infection has been rarely reported.[5,6]

We here report, to the best of our knowledge, the second COVİD-19 patient presenting with AIHA in the absence of an associated underlying disorder.

A 56-year-old male with a medical history of hypertension came to the emergency department with headache, loss of smell and fatigue. He reported contact with a case known to have Covid-19. On physical examination, he had no fever, and his respiratory rate was 12/minute. His oxygen saturation (SpO2) on ambient air was 97%. Reverse transcriptase PCR assay detected the presence of SARS-CoV-2 RNA in the nasopharyngeal swab. Azithromycin 500 mg on day 1 plus 250 mg daily on days 2-5 was started, and the patient was discharged. Four days later, he was admitted to the emergency department with dyspnea, cough, and progressive fatigue. He was subicteric and had tachypnea. His vital signs were as follows: temperature 37.5°C, pulse 112/minute, and respiratory rate of 20 breaths/minute. His SpO2 on ambient air was 91%. On auscultation, breath sounds were reduced with fine bibasilar crackles. Chest computed tomography (CT) showed patchy peripheral ground-glass opacities in both lungs; these findings were compatible with moderate Covid-19 pneumonia (**Figure 1**). Screening for viral respiratory PCR panel, blood, and urine cultures remained negative. Complete blood count showed the following: Hgb 4,3 g/dL, Htc 12%, total leukocyte count 43930/mm^3, neutrophil 35690/mm^3, lymphocyte 4800/mm^3 and platelet count 497,000/mm^3. The following were abnormal on laboratory tests: creatinine 1.81 mg/dl, lactate dehydrogenase (LDH) 2529 U/L (135-248), C-reactive protein (CRP) 21 mg/L (0–5), serum ferritin 3428 ug/L (23-336), total bilirubin 2,95 mg/dl (0-1,2), unconjugated bilirubin 2,27 mg/dl (0-1,2) and haptoglobin 11.5 mg/dl (30-200). D-dimer was increased (4.87 µg/ml; normal range, 0 to 0.5). Our patient had reticulocytosis of 10% (0.60%-1.83%), with an absolute reticulocyte count of 230×10^9/L (29.5-87.3×10^9/L). Peripheral blood smear showed nucleated red blood cells, spherocytes, and polychromasia (**Figure 2**). Direct Coombs test was 4+ for IgG and C3d. Since he had progressive Covid-19 infection, favirapivir 1,600 mg twice daily on day 1, followed by 600 mg twice daily for a total duration of 5 days, was initiated. It was considered that the patient developed secondary AIHA triggered by Covid-19. So, other viral, autoimmune, and malignant diseases were screened and found to be negative. Taking into consideration his active Covid-19 disease, the medical

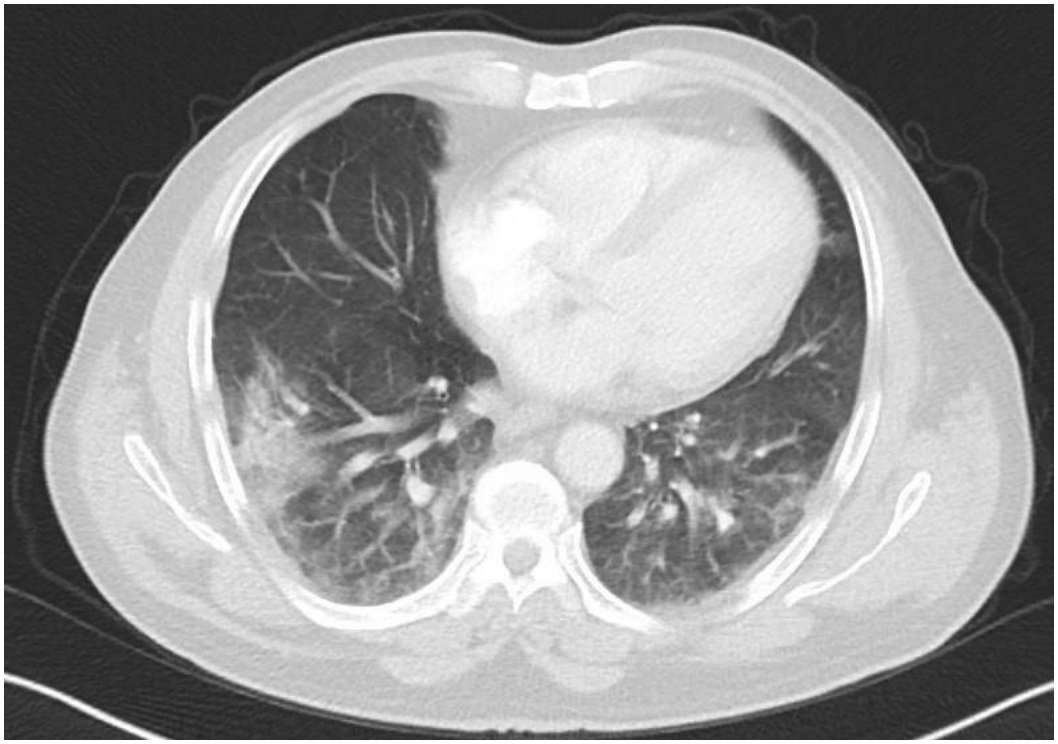

Figure 1. Chest computed tomography shows patchy peripheral ground glass opacities in both lungs, findings compatible with moderate Covid-19 pneumonia.

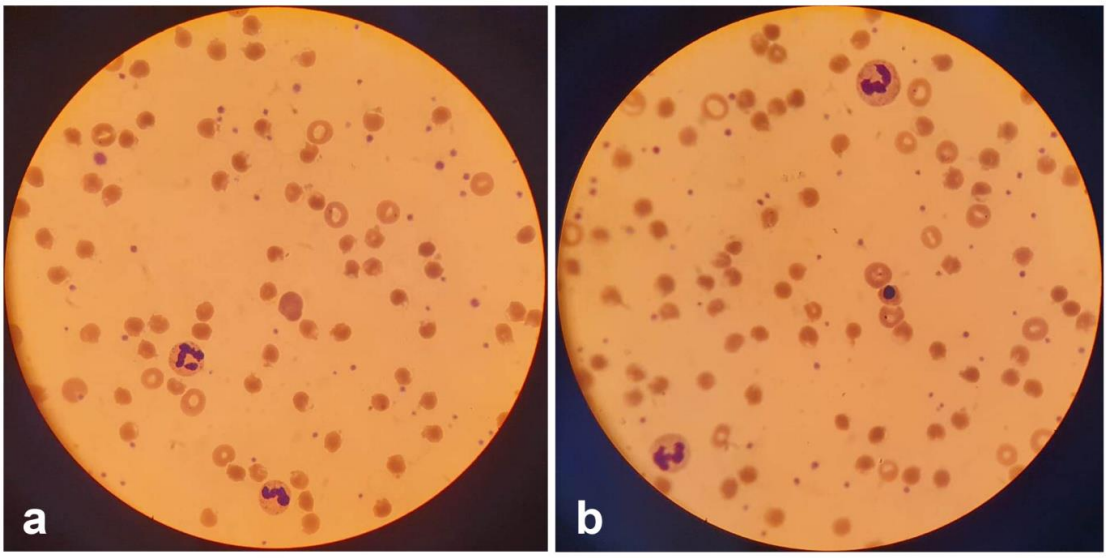

Figure 2. Peripheral blood smear showed spherocytes with **a)** polychromasia and **b)** nucleated red blood cells.

staff administered intravenous immunoglobulin (IVIG) at 1 g/kg/day for two consecutive days to treat the AIHA. However, on the third day of IVIG, the patient remained transfusion dependent with a Hgb of 5 gr/dl. Thus, prednisolone 1 mg/kg/day was started. By the 8th day of prednisolone on day 12 of admission, he was completely transfusion independent and symptom-free with the resolution of his pneumonia. On the day of discharge on the 14th day of admission, his complete blood count was as follows: Hgb 8,5 g/dL, total leukocyte count 12130/mm^3, neutrophil 9800/mm^3, lymphocyte 1450/mm^{3,} and platelet count 437,000/mm^3. At discharge, LDH and unconjugated bilirubin decreased to 600 IU/L and 0,49 mg/dl, respectively. His control nasopharyngeal swab sample for Covid-19was negative. One week after discharge on the 17th day of prednisolone, his Hgb was 10,7 gr/dl. The reticulocyte count and LDH were normal (75×10^9/L and 238 IU/L, respectively). A steroid taper was planned.

Rare cases have been reported in the context of Covid-19.[5,6] Yet, the exact mechanism of the AIHA associated with the novel coronavirus is not known. Lazarian G. et al. reported 7 cases of warm and cold AIHA associated with Covid-19 disease, in which the median time between the first Covid-19 symptoms and AIHA onset was 9 days (range 4 to 13 days).[5] Lopez C. et al. reported another case where AIHA occurred

during the worsening of symptoms of Covid-19 infection.[6] Similarly, our case developed AIHA after the appearance of the symptoms of infection. Furthermore, in accordance with previously reported case series, our patient showed elevated markers of inflammation (i.e., ferritin, CRP, D-dimers) at the time of AIHA onset.[5] We consider that AIHA in our patient was virus-associated and linked with the hyperinflammatory state.

Our patient had a direct Coombs test positive for IgG and C3d. Similarly, Lopez C. et al. reported direct Coombs test positive for IgG and C3 in a Covid-19 patient who had a history of congenital thrombocytopenia.[6] As in our case, warm antibodies were detected in 4 of the 7 cases in the report by Lazarian G. et al..[5] Of the four patients with warm antibodies in the report above, two patients had chronic lymphocytic leukemia, and 1 had IgG kappa monoclonal gammopathy of undetermined significance (MGUS). At that report, only one case with warm autoantibodies had no related hematological disorder.[5] Autoimmune diseases, including systemic lupus erythematosus, other viral pathogens, and malignant disorders as the underlying cause of AIHA, were screened and excluded. We concluded that AIHA in our patient was Covid-19 driven.

The treatment modalities for the four warm AIHA cases in the report of Lazarian G. et al. included corticosteroids (n=3), rituximab (n=1) for corticosteroid failure, and blood transfusion (n=1).[5] Because of the short follow-up period, two of the three patients receiving corticosteroids had been non-evaluable for response.[5] Our patient developed warm antibody AIHA during Covid-19 infection. He had been on azithromycin for four days on admission. Not only azithromycin associated AIHA has not been reported, but also it is unusual for any drug to lead to AIHA in such a short period. Therefore, it is most likely that AIHA in our patient was triggered by Covid-19 infection. In our patient, glucocorticosteroids were not administered as the first choice to treat AIHA since the Centers for Disease Control (CDC) and World Health Organization (WHO) recommended against the use of glucocorticoids in Covid-19 patients because of the potential immunosuppressive effect of steroids and their potential to decrease viral shedding.[7] Thus, we administered IVIG as 1st line treatment to treat AIHA. However, our patient did not respond to IVIG, a finding consistent with the current guidelines regarding the therapy of AIHA, which report a scarce response to IVIG.[8] In line with our observation, Lopez C. et al. reported a case with no response to IVIG.[6] In our patient, Hgb levels stabilized and improved under prednisolone. Partial response, defined by Hgb greater than 10 g/dl with no need of transfusion, was achieved. Rituximab treatment could also be considered in unresponsive patients.

To the best of our knowledge, eight cases with AIHA and Covid-19 have been reported.[5,6] Seven of these cases have a related pathology (chronic lymphocytic leukemia (n=2), marginal zone lymphoma (n=2), MGUS (n=1), prostate cancer (n=1) and congenital thrombocytopenia (n=1) that may be associated with AIHA.[5,6] Only one of the reported patients had no underlying pathology. Our case is the second Covid-19 case with AIHA with no underlying disorder.

Glucocorticoids are considered the mainstay of treatment of newly diagnosed primary AIHA,[8] but they have a dubious effect on the outcome of Covid-19. Recent reports have reported good outcomes in Covid-19 patients with corticosteroids suggesting that corticosteroids may prevent the progression of Covid-19 disease to severe hyperreactive forms. These findings supported the use of steroids in the early acute phase of Covid-19.[9-11] Authors, however, emphasize that specific studies are warranted to confirm this hypothesis. On the other hand, 'WHO' does not currently recommend corticosteroids in viral diseases, including Covid-19 as the glucocorticoid-mediated stimulation of the hypothalamic-pituitary-adrenal axis can also drive lymphopenia, or it may promote exaggerated pro-inflammatory responses that eventually result in worsening of the pathogenic condition. The Randomised Evaluation of Covid-19 (RECOVERY) trial compared anti-inflammatory steroid (dexamethasone) with lopinavir/ritonavir, hydroxychloroquine, and azithromycin and reported that dexamethasone causes a reduction of the mortality of 30% in Covid-19 patients requiring ventilation or oxygen.[12] Our findings imply that corticosteroids could be used with success in AIHA triggered by Covid-19, and corticosteroids should be tapered after stabilization of the blood count. He showed marked response to corticosteroids after failure to IVIG with no adverse events attributed to corticosteroids and with a favorable evolution of lung involvement.

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References:

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J et al. China Novel Coronavirus I, Research T: A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020 Feb; 382(8): 727-33. https://doi.org/10.1056/NEJMoa2001017 PMid:31978945 PMCid:PMC7092803
2. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG et al. Guillain-Barré Syndrome Associated with SARS-CoV-2. N Engl J Med. 2020 Apr; 17:NEJMc2009191. https://doi.org/10.1056/NEJMc2009191 PMid:32302082 PMCid:PMC7182017
3. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N Engl J Med. 2020 Apr;382(17):e38. https://doi.org/10.1056/NEJMc2007575 PMid:32268022 PMCid:PMC7161262
4. Zulfiqar A-A, Lorenzo-Villalba N, Hassler P, Andrès E. Immune Thrombocytopenic Purpura in a Patient with Covid-19. N Engl J Med. 2020 Apr;382(18):e43. https://doi.org/10.1056/NEJMc2010472 PMid:32294340 PMCid:PMC7179995
5. Lazarian G, Quinquenel A, Bellal M, Siavellis J, Jacquy C, Re D et al. Autoimmunehemolyticanemiaassociated with Covid-19infection. Br J Haematol. 2020 May 6. doi: 10.1111/bjh.16794. Online ahead of print. https://doi.org/10.1111/bjh.16794 PMid:32374906 PMCid:PMC7267601
6. Lopez C, Kim J, Pandey A, Huang T, DeLoughery TG. Simultaneous Onset of COVID-19 and Autoimmune Haemolytic Anaemia. Br J Haematol. 2020 May 5. doi: 10.1111/bjh.16786. https://doi.org/10.1111/bjh.16786 PMid:32369626 PMCid:PMC7267644
7. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease2019 (COVID-19): A Review. JAMA. 2020 Apr 13. doi: 10.1001/jama.2020.6019. https://doi.org/10.1001/jama.2020.6019
8. Lechner K, Jager U. How I treat autoimmune hemolytic anemias in adults. Blood. 2010 Sep; 116 (11):1831-8. https://doi.org/10.1182/blood-2010-03-259325 PMid:20548093
9. Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? Ecancermedicalscience. 2020 Mar;14:1023. https://doi.org/10.3332/ecancer.2020.1023
10. Dai J, Xiong Y, Li H, Qian Y, Xu Y, Xu Qet al. Corticosteroid treatment in severe COVID-19 pneumonia: two cases and literature review. Clin Rheumatol.2020 Jul;39(7):2031-7. https://doi.org/10.1007/s10067-020-05172-7 PMid:32451729 PMCid:PMC7247779
11. Gazzaruso C, Carlo Stella N, Mariani G, Tamburlini A, Garini P, Freddi E et al. Impact of anti-rheumatic drugs and steroids on clinical course and prognosis of COVID-19. Clin Rheumatol. 2020 Jun;17: 1-3. https://doi.org/10.1007/s10067-020-05239-5
12. Biggest COVID-19 trial tests repurposed drugs first. Nat Biotechnol. 2020 May;38(5):510 https://doi.org/10.1038/s41587-020-0528-x PMid:32393915