TMCR-2020-0174 Received: 24-Dec-2020; Accepted: 2-Sep-2021

Case Report

COVID-19 and Adult-onset Still's Disease as part of Hyperferritinemic Syndromes

Tatsuya Kawasaki*, Seido Ooka*, Machiko Mizushima*, Yuta Nakamura**, Hiroki Ikeda**, Tsutomu Sakurada**, Shotaro Suzuki*, Kazuko Yamazaki*, Yutaka Goto*, Keiichi Sakurai*, Yamasaki Yukitaka***, Tomofumi Kiyokawa*, Kumiko Tonooka*, Hiroyuki Kunishima***, Kimito Kawahata*

* Division of Rheumatology and Allergology Department of Internal Medicine, St. Marianna University School of Medicine, Kanagawa, Japan

** Department of Internal Medicine, St. Marianna University School of Medicine, Kanagawa, Japan

*** Department of Infectious Diseases, St. Marianna University School of Medicine, Kanagawa, Japan

Corresponding author: Seido Ooka,

Division of Rheumatology and Allergology, St. Marianna University School of Medicine,

Kawasaki city, Kanagawa 216-0015, Japan

Tel +81 44 977 8111, Fax +81 44 977 8593. Email: ooka@marianna-u.ac.jp

Abstract

The coronavirus disease (COVID-19) is known to cause hyperferritinemia and hemophagocytic lymphohistiocytosis (HLH). Including this laboratory parameter, clinical

symptoms similar to COVID-19 have been observed in adult-onset Still's disease (AOSD), catastrophic antiphospholipid syndrome (CAPS), macrophage activation syndrome (MAS), and septic shock, which has led to the proposal of a concept called "hyperferritinemic syndromes." Additionally, high levels of some clinical markers in both COVID-19 and AOSD make them difficult to differentiate. While the efficacy of ciclesonide had been expected for mild pneumonia with COVID-19, the efficacy of tocilizumab, which is a known treatment for AOSD, was not established. Here, we report the first known occurrence of COVID-19, diagnosed in March 2020, preceded by the diagnosis of AOSD, in April 2019, in a 65-year-old, otherwise healthy man. Following the diagnosis of the latter, the patient was first given prednisolone and then tocilizumab, which led to remission. With the recurrence of joint pain and rash in March 2020, accompanied by low oxygen saturation levels (90%), and ground-glass appearance on chest CT, PCR test revealed COVID-19 infection. Ciclesonide was started on day 7 of the disease onset, which led to improved inflammatory markers by day 21. Thus, we infer that while tocilizumab is theoretically useful for COVID-19 due to its inhibition of interleukin 6 (IL-6), additional ciclesonide therapy might be required to prevent worsening of the condition. AOSD and COVID-19 must, therefore, be differentiated by levels of ferritin which differ between the two, and appropriate treatment must be allocated.

Keywords: COVID-19, Adult onset still's disease, hyperferritinemia, tocilizumab, cyclesonide

Introduction

The novel coronavirus disease (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)". COVID-19, a disease for which many cases are subclinical infections, is reportedly spread even by asymptomatic carriers [1,2], and it is also difficult to prevent the infection itself [3]. There have been cases that deteriorate rapidly during the early stages of the disease [4], which makes early detection and prevention of progression important for controlling COVID-19.

Approximately 20% of those infected with COVID-19 develop severe conditions, and approximately 3% of them die. Along with age, underlying disease(s) and smoking, clinical laboratory parameters such as reduced lymphocyte count, high ferritin values, and high C-reactive protein (CRP) levels are known to be factors correlated with the development of severe COVID-19 infections [4-9], but it is unclear whether these can predict the prognosis. Some COVID-19 infections cause hyperferritinemia, and present with hemophagocytic lymphohistiocytosis (HLH). Including the hyperferritinemia that develops in association with such cases of severe COVID-19 infections, similar clinical

symptoms and laboratory findings have been observed in adult-onset Still's disease (AOSD), catastrophic antiphospholipid syndrome (CAPS), macrophage activation syndrome (MAS), and septic shock, which has led to the proposal of a concept called "hyperferritinemic syndromes" [10].

At present, there are very few reports of patients with both COVID-19 and collagen diseases. In particular, there have been no reports of COVID-19 in AOSD cases. AOSD is a disease characterized by fever, sore throat, rash, and joint pain, and laboratory findings often indicate elevated inflammatory markers and high ferritin levels. It is a type of hyperferritinemic syndrome in which cytokine storms develop, which activate macrophages, and around 3% of patients present with HLH [11].

Even though the frequencies of COVID-19 and AOSD as parts of hyperferritinemic syndromes differ, commonalities such as fever, sore throat, joint pain, and rash as symptoms as well as high inflammatory markers in laboratory findings, highly elevated ferritin and interleukin 2 receptor (IL-2R), among others, and high levels of their clinical markers make it difficult to distinguish between the two (Table 1).

Even though some treatments such as dexamethasone [12] have been shown to be effective for treating COVID-19, there is yet to be an established treatment for the infection. There are many candidates including Remdesivir [13-15], Kaletra [16], and Chloroquine [17], but their therapeutic effects remain unclear.

It has been reported that peripheral blood of severe COVID-19 patients shows decreased cluster of differentiation (CD) 4 and CD8-positive T cells and increased T helper cell 17 (Th17) levels [18]. Some reports indicate that decreasing CD8-positive cells with age is a risk factor for the development of severe COVID-19 infection [19]. Elevated Th17 as a response to systemic pathology of severe COVID-19, and enhancement of interleukin (IL) 17-related pathways are known to be significantly involved in the pathology of COVID-19 [20], but as tocilizumab suppresses Th17 by blocking IL6, it is regarded as a candidate drug for the treatment of COVID-19 [21].

On the other hand, some cases of AOSD reportedly present with high IL6 and high tumor necrosis factor (TNF) α levels, and tocilizumab has already been established as a treatment for this condition [22].

We have previously reported the efficacy of ciclesonide treatments for controlling the development of severe COVID-19 infections [23]. ciclesonide is an inhaled steroid that has been approved as a treatment for asthma, but it has been shown to exhibit in vitro antiviral effects [24].

On this occasion, we encountered a case of one AOSD patient who developed COVID-19 while receiving tocilizumab treatment, whose condition improved without becoming severe after receiving ciclesonide treatment. We are reporting this clinical experience as a useful example for future treatments, having been able to prevent the deterioration of

the COVID-19 infection by controlling the two diseases that are known to exhibit hyperferritinemic syndrome. About this case report, we obtained informed consent from this patient in writing.

Case presentation

A 65-year-old previously healthy man consulted our hospital after experiencing fever, joint pain, and urticaria-like rash in April 2019. Laboratory findings indicated an elevated white blood cell count of 17,000 /mm^3, predominantly neutrophils as well as high CRP level of 8.24 mg/dL. The patient also had high ferritin levels at 637 ng/mL, and was negative for rheumatoid factors. We checked negative for blood cultures. We also checked for tuberculosis, syphilis, HIV, and hepatitis viruses and confirmed negative. To search for malignancy, we performed contrast-enhanced CT scan of the whole body, esophagogastroduodenoscopy and total colonoscopy and confirmed that there were no findings of malignancy. That led him to be diagnosed with AOSD. After starting treatment with prednisolone (PSL) 60 mg, the symptoms improved rapidly. As reducing the PSL dose led to recurrence of the symptoms, he began receiving tocilizumab (8 mg/kg every 4 weeks) from October 2019. The patient's condition went into remission after these treatments, as indicated by normalization of symptoms, inflammatory responses, and ferritin levels. By February 2020, the patient's PSL dose could be reduced to 9 mg. Due to the reappearance of fever and joint pain from March 17th, the patient visited our hospital again for examination. The last dose of tocilizumab was given on March 8th, 9 days before. CRP was consistently below the sensitivity of measurement. We noted the patient's reduced blood oxygenation levels based on an oxygen saturation of approximately 90% in room air, and chest computed tomography scans(CT) revealed ground glass opacity in both lungs (Figure 1). PCR tests revealed that the patient was positive for SARS-CoV-2, and he was subsequently diagnosed with COVID-19 infection. As the patient's lymphocyte count was low, at 765/mm^3, and the ferritin levels had increased to 960 ng/mL, we anticipated that his condition could become severe. Hence, we started the patient on ciclesonide treatment from Day 7 of disease onset. Although the patient's oxygenation levels deteriorated to O_2 cannula max. 5L/min., this improved afterwards to the point that the patient no longer required oxygen administration on Day 9. By Day 21 of disease onset, the lymphocyte count and ferritin levels had improved to 1,330/mm^3 and 388 ng/mL, respectively. Lemdesivir was not administered throughout the treatment period.

Discussion

In this case, an AOSD patient developed COVID-19 while receiving tocilizumab treatment, and his condition improved after receiving ciclesonide treatment.

The major severe pathologies of COVID-19 include HLH associated with cytokine storm, respiratory failure, and pulmonary embolism associated with thrombotic tendencies. The pathology of HLH associated with COVID-19 is known to be very severe, often involving inflammatory responses as well as high ferritin and IL-2R levels [25]. On the other hand, AOSD is a disease accompanied by fever, pharyngeal pain, joint pain, and sometimes lung lesions and blood cell depletion against the background of cytokine storms of unknown cause, and involves cytokines such as IL-6, IL-8, IL-18, TNFα, interferon (INF) γ, IL-2R, and macrophage-colony stimulating factor [26]. These reports suggest that COVID-19 and AOSD share common pathologies of cytokine storms and hyperferritinemia. Both diseases, as parts of hyperferritinemic syndromes, present with elevated ferritin levels, but some reports indicate that 99/165 (60.0%) cases with AOSD have ferritin levels greater than 3,000 ng/mL [11], while others indicate that a cut-off level of 1,250 ng/mL provides higher sensitivity and specificity [27]. Conversely, reports indicate that the mean ferritin levels in COVID-19 cases is 662.4 ng/mL (interquartile range: 380.9 to 1,311.9 ng/mL) [28], which suggests that AOSD and COVID-19 differ in terms of the increase in ferritin levels.

Other reports indicate that the significant reduction in CD4+ T cells, CD8+ T cells, CD3 cells, CD19 cells, and natural killer (NK) cells as well as elevated ferritin, IL-2R, IL-4, IL-6, IL-8, IL-10, TNFα, and INFγ are factors related to the development of severe COVID-19 infection [29]. In the present case as well, we noted elevated ferritin, CRP, and IL-2R levels, indicating hyperferritinemia due to COVID-19 or AOSD. If we take into consideration the fact that the patient's maximum ferritin level was 960 ng/mL and below the cut-off of 1,250 ng/mL, absence of rash, which has a low prevalence in COVID-19 but is frequently observed in AOSD, and improvement of conditions following ciclesonide treatment, it is likely that the hyperferritinemia exhibited by the present patient was due to COVID-19.

It has been reported that reduced CD4+ and CD8+ T cells and increased Th17 is seen in the peripheral blood of patients with severe COVID-19 infections [18], and that elevated Th17 response to the systemic pathology of severe COVID-19 and upregulation of IL-17-related pathways are significantly involved in the pathology of the disease [20]. As tocilizumab inhibits IL-6, which is necessary for the differentiation of immature helper T cells into Th17, this drug may contribute to stopping the infection from becoming severe.

Unfortunately, we have not performed blood cell isolation on this patient and have not been able to determine the character of the lymphocytes in the blood. However, with the administration of TCZ, AOSD has remained in remission, with no flare-ups of arthritis or skin rash, and CRP has always been below the sensitivity of the measurement, even

during the infection with COVID-19 since the last dose of TCZ.

We infer from the clinical symptoms that the cytokines involved in AOSD, especially IL-6, were well controlled. As the present patient had been receiving tocilizumab treatment for AOSD, it may have led to halting the cytokine storm associated with COVID-19, thereby preventing the infection from becoming severe.

The present patient, who could be treated without the COVID-19 infection becoming severe, had been receiving anti-cytokine treatments using tocilizumab. It is unclear whether AOSD treatments using tocilizumab had an impact or ciclesonide treatment after COVID-19 onset was successful. Furthermore, while cytokine markers such as IL-2R, CRP, and ferritin were elevated, we did not measure the actual levels of cytokines.

In order to prevent a patient with COVID-19 and AOSD, which are part of the hyperferritinemic syndromes, from developing severe symptoms, it is necessary to diagnose and distinguish between the two from the early stages and start treatment early. Furthermore, we believe that controlling hyperferritinemic syndrome, which is a severe pathology of COVID-19, is one of the keys to reducing the mortality rate of COVID-19.

Figure Legend

Chest CT on Day 4 spotted multiple ground glass opacity in both lungs.

Table 1

N/A: not applicable

Acknowledgments

We thank all medical staff who treated COVID-19 with us.

We would like to thank Editage (www.editage.com) for English language editing.

Conflict of interest: None.

Ethical Approval: Not applicable

References

1. Li G, Li W, He X, Cao Y. Asymptomatic and Presymptomatic Infectors: Hidden Sources of COVID-19 Disease. Clin Infect Dis. 2020;71:2018.
2. Wei WE, Li Z, Chiew CJ, et al. Presymptomatic Transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:411–415.
3. Liu Y, Gayle AA, Wilder-Smith A, et al. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;27.
4. Wang Y, Lu X, Chen H, et al.. Clinical Course and Outcomes of 344 Intensive Care Patients with COVID-19. Am J Respir Crit Care Med. 2020.
5. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020.
6. Liu Y, Liao W, Wan L, et al. Correlation Between Relative Nasopharyngeal Virus RNA Load and Lymphocyte Count Disease Severity in Patients with COVID-19. Viral Immunol. 2020.
7. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol. 2020.
8. Henry BM, de Oliveira MHS, Benoit S, et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020.
9. Henderson LA, Canna SW, Schulert GS, et al. On the alert for cytokine storm: Immunopathology in COVID-19. Arthritis Rheumatol. 2020.
10. Colafrancesco S, Alessandri C, Conti F, et al. COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome? Autoimmun Rev. 2020;19:102573.
11. Asanuma YF, Mimura T, Tsuboi H, et al. Nationwide epidemiological survey of 169 patients with adult Still's disease in Japan. Mod Rheumatol. 2015;25:393–400.

12. Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020.
13. Agostini ML, Andres EL, Sims AC, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. mBio. 2018;9.
14. Ko WC, Rolain JM, Lee NY, et al. Arguments in favour of remdesivir for treating SARS-CoV-2 infections. Int J Antimicrob Agents. 2020;55:105933.
15. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9.
16. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020.
17. Cortegiani A, Ingoglia G, Ippolito M, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care. 2020.
18. De Biasi S, Meschiari M, Gibellini L, et al. Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. Nat Commun. 2020;11:3434.
19. Rydyznski Moderbacher C, Ramirez SI, Dan JM, et al. Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. Cell. 2020;183:996-1012 e19.
20. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. J Microbiol Immunol Infect. 2020;53:368-70.
21. Zhang C, Wu Z, Li JW, et al. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55:105954.
22. Kaneko Y, Kameda H, Ikeda K, et al. Tocilizumab in patients with adult-onset still's disease refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial. Ann Rheum Dis. 2018;77:1720–1729.
23. Yamasaki Y, Ooka S, Tsuchida T, et al. The peripheral lymphocyte count as a predictor of severe COVID-19 and the effect of treatment with ciclesonide. Virus Res. 2020;290:198089.
24. Meehyun Ko SYC, Byun SY, Choi I, et al. Screening of FDA-approved drugs using a MERS-CoV clinical isolate from South Korea identifies potential therapeutic options for COVID-19. bioRxiv. 2020.

25. Mehta Y, Dixit SB, Zirpe KG, et al. Cytokine Storm in Novel Coronavirus Disease (COVID-19): Expert Management Considerations. Indian J Crit Care Med. 2020;24:429–434.

26. Choi JH, Suh CH, Lee YM, et al. Serum cytokine profiles in patients with adult onset Still's disease. J Rheumatol. 2003;30:2422–2427.

27. Lian F, Wang Y, Yang X, et al. Clinical features and hyperferritinemia diagnostic cutoff points for AOSD based on ROC curve: a Chinese experience. Rheumatol Int. 2012;32:189–192.

28. Qin C, Zhou L, Hu Z, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71:762–768.

29. Akbari H, Tabrizi R, Lankarani KB, et al. The role of cytokine profile and lymphocyte subsets in the severity of coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Life Sci. 2020;258:118167.

Figure 1

Figure 2

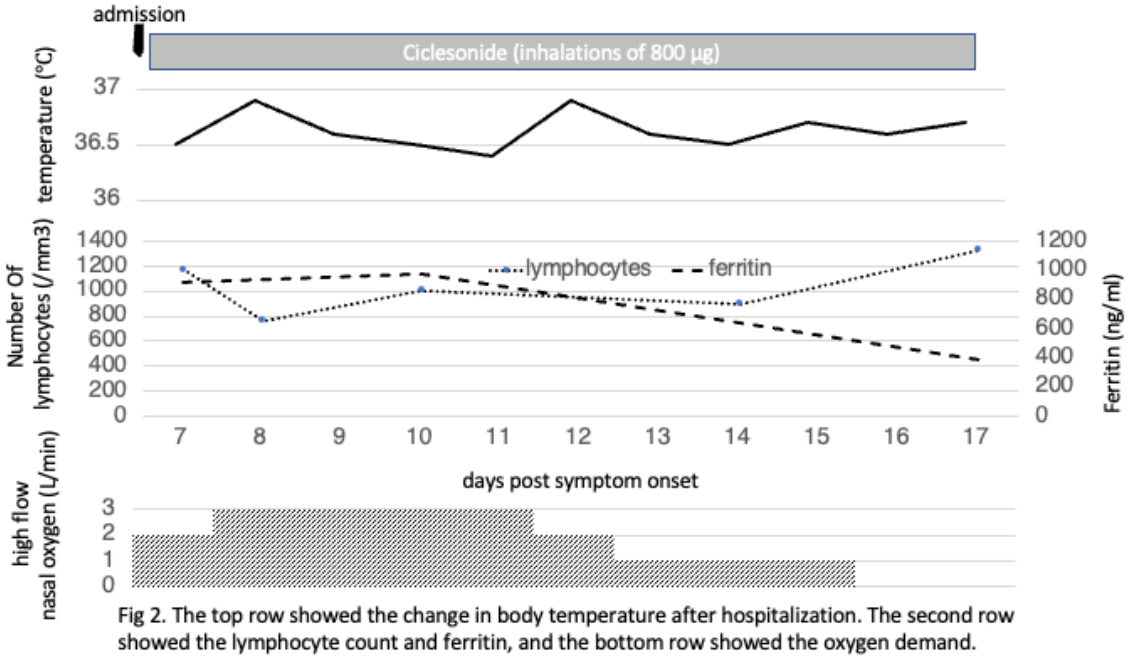

Fig 2. The top row showed the change in body temperature after hospitalization. The second row showed the lymphocyte count and ferritin, and the bottom row showed the oxygen demand.

Table 1

	Country	Fever	Arthralgia	Arthritis	Myalgia	rash	Sore throat	Lymph-adenopathy	Pericarditis	Pleuritis	Interstitial pneumonia	Reference
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
AOSD	Jspan	152/166 (91.6%)	138/166 (83.1%)	77/152 (50.7%)	42/162 (25.9%)	102/164 (62.2%)	96/162 (59.3%)	72/161 (44.7%)	5/161 (3.1%)	6/161 (3.7%)	4/161 (2.5%)	(11)
COVID-19	Japan	118/187 (63.1%)	N/A		12/187 (6.4%)	N/A	32/187 (17.1%)	N/A	N/A	N/A	N/A	(33)
	China	975/1099 (88.7%)		164/1099 (14.9%)		2 /1099 (0.2%)	153/1099 (13.9%)	N/A	N/A	N/A	N/A	(34)
	China							237/4081 (5.81%)	17/561 (3.03%)	182/4181 (4.35%)	2650/4624 (57.31%)	(35)