SAGE Open Medical Case Reports
Volume 12: 1–5

DOI: 10.1177/2050313X241233197
journals.sagepub.com/home/sco
Sage

Association between adult-onset still's disease and COVID-19: A report of two cases and brief review

Sarah Fet-He[1], Gabriel Ibarra Lecompte[1] and Alejandro José Quiroz Alfaro[2]

Abstract

Adult-onset still's disease is a rare multisystemic autoinflammatory disorder with an estimated annual incidence of 0.16–0.62 per 100,000 individuals worldwide. It is typically considered a diagnosis of exclusion. SARS-CoV-2 is a positive-strand RNA virus that causes the acute respiratory infection known as COVID-19. Although COVID-19 predominantly affects the respiratory system, it has also been proposed as a trigger for autoimmune diseases, like adult-onset still's disease, as both share considerable pathophysiological similarities. We report two cases of patients with adult-onset still's disease, where COVID-19 was the most likely cause for a flare-up in the first case and the most likely trigger for adult-onset still's disease in the second case. Although the exact mechanism is not entirely understood, the similarities between adult-onset still's disease and COVID-19 could indicate a shared underlying mechanism explaining why COVID-19 can lead to adult-onset still's disease or worsen its symptoms. Further research is necessary to fully comprehend the intricate connections between the two conditions and their immunological effects.

Keywords

COVID-19, adult-onset still's disease, autoinflammatory disorder, exclusion diagnosis, autoimmunity trigger

Date received: 14 October 2023; accepted: 29 January 2024

Introduction

Adult-onset still's disease (AOSD) is a rare multisystemic autoinflammatory disorder with an estimated annual incidence of 0.16–0.62 per 100,000 individuals worldwide.[1] AOSD is typically considered a diagnosis of exclusion while investigating a patient with a fever of unknown origin; patients often present with a transient nonpruritic maculopapular salmon-colored rash, spiking daily fevers, arthralgia or arthritis, and elevated acute-phase reactants.[1]

SARS-CoV-2 is an enveloped, positive-strand RNA virus from the Coronaviridae family that causes the acute respiratory infection known as COVID-19.[2] Although COVID-19 predominantly affects the respiratory system, it also commonly involves other organs and has been proposed as a trigger for autoimmune diseases like multiple sclerosis, vasculitis, and hemolytic anemia.[3]

COVID-19 and AOSD share considerable pathophysiological similarities, including systemic inflammation, elevated ferritin, fever, and significant organ involvement in the case of severe COVID-19.[4] We present two cases of patients with AOSD, where COVID-19 was the most likely cause for a flare-up in the first case and the most likely trigger for AOSD in the second case.

Case presentations

First case

A 29-year-old female patient presented to the emergency department with dyspnea after testing positive for COVID-19 on a home test. She had a week of constant and

[1]Brown University, Providence, RI, USA
[2]Universidad Colegio Mayor de Nuestra Señora del Rosario, Bogotá, Colombia

Corresponding Author:
Alejandro José Quiroz Alfaro, Universidad Colegio Mayor de Nuestra Señora del Rosario, Cra. 19 #4c-72, Clínica Erasmo, Valledupar 200005, Colombia.
Emails: alejandro.quiroz@urosario.edu.co; quirozq@outlook.com

Table 1. Laboratory tests results.

Days since emergency department visit	Day 0	Day 1	Day 2	Day 3
WBC (10^9/L)	23.8	22.4		12.2
Hemoglobin (g/dL)	10.6	8.7		9.0
Platelets (10^9/L)	329	275		242
Ferritin (ng/mL)		1005	1,520	549
ESR (mm/h)		42/37*		
CRP (mg/L)		191/188*	212	70

WBC: white blood cells; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.
*Repeated on same day.

progressively worsening fever, headache, generalized myalgias, polyarthralgia, nausea, emesis, and pharyngitis.

Of note, she was diagnosed a few months prior with AOSD and CREST syndrome after extensive work-up by her rheumatologist in her home state. She was diagnosed with CREST in the setting of occasional Raynaud's, though at the time of admission, she did not display any active skin manifestations. She initially was taking 10–20 mg of prednisone for her AOSD but was taken off this steroid a month before presenting to the emergency room due to increasing edema. She was subsequently prescribed dexamethasone 8 mg, which she stopped taking 1–2 weeks before her hospital visit as it caused her facial edema.

At the time of presenting to the emergency room, she managed her AOSD with Anakinra 100 mg once daily injections and methotrexate 10 mg per week, which she began 1 month before the hospital visit. On this regimen, her symptoms were well controlled, with just some low-grade arthralgia and muscle stiffness. The pain she experienced during her hospital visit reflected an acute change of increased pain that occurred 72 h before admission. This pain was associated with fever spikes, rigors, and maculopapular skin rashes that appeared on her chest and thighs and faded on their own.

In the emergency department, the patient was tachycardic up to 130 beats per min, febrile to 39.4°C, and normoxic. The rest of the physical exam was unremarkable. Lab work was notable for leukocytosis with a white blood cell count of 23.8×10^9/L, microcytic anemia with a hemoglobin of 10.6 g/dL and a mean corpuscular volume (MCV) of 71.5 fL, a D-dimer of 2500 ng/mL, and a positive COVID-19 test. Additionally, CT angiography of the lungs demonstrated that the patient did not have a pulmonary embolism or focal consolidations. Instead, the patient had extensive supradiaphragmatic adenopathy in the mediastinal, hilar, and paratracheal spaces with splenomegaly. Concerns for lymphoma were ruled out, given the patient's extensive history of diffuse lymphadenopathy and a recent biopsy of the right supraclavicular lymph node, which was negative for lymphoma.

Upon admission, the patient was treated for an AOSD flare, given her constellation of symptoms. She was started on intravenous methylprednisolone 150 mg every 8 h and dexamethasone 12 mg once daily. Her Anakinra and methotrexate were held. Her dyspnea, likely secondary to COVID-19 infection, resolved early in her hospital course. Nevertheless, the consulted rheumatologist endorsed using intravenous remdesivir 100 mg to treat the patient's extrapulmonary manifestations of COVID-19.

The patient maintained a high white blood cell count during her hospital stay. Her lactate dehydrogenase (LDH) was elevated at 398 U/L, and her liver function tests remained within normal limits. She also had elevated inflammatory markers such as high C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin (Table 1).

Upon being treated for an AOSD flare with the steroid regimen explained above, the patient reported symptomatic improvement with improving polyarthralgia, decreased fevers, and an increase in appetite. She was subsequently discharged on 20 mg of dexamethasone daily for 2 weeks and her previous doses of Anakinra and methotrexate. She remained stable when followed up a month later.

Second case

A 55-year-old female patient with a past medical history of type 2 diabetes mellitus and hypothyroidism presented to the emergency room with fever, malaise, sore throat, and polyarthralgia. She denied any rashes. Two weeks prior, she had tested positive for COVID-19 and initiated treatment with Paxlovid (nirmatrelvir/ritonavir). On the third day of treatment, she developed myalgias and daily fevers of 39°C associated with the abovementioned symptoms.

On admission, she was afebrile and tachycardic but otherwise stable. Laboratory workup demonstrated leukocytosis (17.8×10^9/L) with neutrophilia (91%). She had persistent fevers of up to 39°C throughout her admission and demonstrated elevated ferritin, ESR, and CRP levels (Table 2).

She additionally had an elevated D-dimer at 859 ng/mL. Extensive infectious workup yielded negative results for various pathogens, including HIV, hepatitis A, B, and C, a respiratory viral panel, Epstein–Barr virus, parvovirus B19, tuberculosis, Lyme disease, Anaplasma, Bartonella, Babesia, anti-treponemal antibodies, and negative blood cultures. Although her Cytomegalovirus IgG was positive, the IgM was not elevated.

Her creatinine kinase, complement C3/C4 levels, liver function, and renal function tests were normal. She did not have signs of vasculitis or any other symptoms, and her autoimmune workup was also unremarkable, apart from positive antinuclear antibodies (ANAs), in the context of hypothyroidism. She was negative for rheumatoid factor (RF), lupus anticoagulant, anticardiolipin antibodies, anti-beta-2 glycoprotein, antineutrophil cytoplasmic antibodies, anti-double-stranded DNA, and antinuclear ribonucleoprotein.

Cross-sectional imaging studies revealed scattered cervical lymphadenopathy and hepatosplenomegaly. Given the concern for AOSD, treatment was initiated with oral prednisone

Table 2. Laboratory tests results.

Days since emergency department visit	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
WBC (10^9/L)	17.8	16.9	13.0		15.0		9.2
Hemoglobin (g/dL)	13.1	11.3	12.0		11.1		11.2
Platelets (10^9/L)	319	295	315		313		241
Ferritin (ng/mL)						12,189	9,404
ESR (mm/h)						82	
CRP (mg/L)			198.99		189.31	198.63	

WBC: white blood cells; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

60 mg daily and gradually tapered as her symptoms improved. During a follow-up, a month later, she remained stable without any fevers since starting prednisone inpatient, and Canakinumab therapy is being considered to treat her AOSD.

Discussion

Yamaguchi et al.[5] proposed one of the most widely used diagnostic classifications for this condition. It consists of four major criteria: fever ⩾39°C for at least 1 week, arthralgias or arthritis lasting ⩾2 weeks, a nonpruritic salmon-colored macular or maculopapular rash over the trunk or extremities that usually accompanies the fever, and leukocytosis ⩾10,000/mL with ⩾80% granulocytes. Additionally, there are five minor criteria: sore throat, lymphadenopathy, hepatomegaly or splenomegaly, abnormal liver function tests, and negative ANA and RF antibodies. Diagnosing AOSD requires the presence of five or more criteria, including at least two of the major criteria. Although this classification has a sensitivity of 96.2% and specificity of 92.1%, other criteria have also been used historically; nonetheless, a definitive "gold standard" diagnostic workup or test is yet to be determined.[1]

Previous case reports suggest potential overlapping signs and symptoms between AOSD and COVID-19, including lung lesions, fever, sore throat, and joint pain.[4] However, we argue that both patients' constellation of symptoms met the criteria for AOSD, demonstrating AOSD triggered by COVID-19 infection rather than COVID-19 infection alone. In the case of our first patient, she met two major Yamaguchi et al.[5] criteria as she had maculopapular rashes associated with high fevers and leukocytosis with ⩾80% neutrophils. She also met three minor criteria, given her sore throat, lymphadenopathy, and splenomegaly. Additionally, her symptoms while admitted were similar to those she experienced months prior when she was first diagnosed with AOSD, and she improved with steroids.

In the case of our second patient, she met two major Yamaguchi et al.[5] criteria (fever ⩾39°C for at least 1 week and leukocytosis with neutrophilia) and three minor criteria (sore throat, lymphadenopathy, and hepatosplenomegaly) after the COVID-19 diagnosis. Our second patient also improved after therapy with steroids.

Although the pathogenesis of AOSD is unclear, the clinical manifestations of the disease correspond with cardinal features of a systemic autoinflammatory disease, implying that the innate immune system and the resultant pro-inflammatory cascade play a central role in disease pathogenesis.[6] Therefore, a postulated mechanism for the pathogenesis of AOSD is that external factors, such as pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns, trigger the activation of innate cells such as macrophages and neutrophils through toll-like receptors.[7] The mechanism mentioned above activates specific inflammasomes, resulting in caspase activation and overproduction of IL-1β, which amplifies the immune response.[7] This amplification of the immune response is an event observed in the pathogenesis of both COVID-19 and AOSD.

Additionally, evidence in the literature shows elevated levels of ferritin, interleukin (IL)-1, interleukin 2 receptor (IL-2R), IL-6, IL-8, TNFα, and interferon (INF) γ during the hyperinflammatory response triggered by severe COVID-19.[4,8] These inflammatory markers and cytokines are also elevated in AOSD.[4,8] Interestingly, both of our patients also presented leukocytosis and elevated ferritin levels.

Current literature on the pathogenesis of AOSD endorses the role of PAMPs from bacteria or viruses as a potential trigger for the inflammatory cascade thought to be characteristic of AOSD. There are reports of cases of AOSD after viral infection with viruses like rubella, measles, Epstein–Barr virus, hepatitis A, B, and C, HIV, and cytomegalovirus.[6] Similarly, AOSD has been associated with bacterial infections with bacteria like *Yersinia enterocolitica*, *Campylobacter jejuni*, *Chlamydia trachomatis*, and *Borrelia burgdorferi*.[6] Although the associations exist, it is still unknown whether infection with these pathogens is directly responsible for developing rather than triggering AOSD.[7] Based on our findings, most of the evidence on the subject supports that these infections are more likely to act as a trigger.

The resemblance in the inflammatory markers and cytokine profiles of AOSD and COVID-19 suggests potentially shared underlying pathogenic mechanisms between the two conditions. Several authors have proposed that a misdirected inflammatory response against SARS-CoV-2 could trigger the

onset of AOSD.[8,9] This misdirected inflammatory response may have precipitated a flare-up in our first patient and most likely triggered the onset of AOSD in our second patient, respectively. We also ruled out other differential diagnoses for both cases, including infections, malignancy, and other autoimmune diseases, and the first patient's flare-up occurred despite prior control with methotrexate and Anakinra, supporting that COVID-19 was the most likely precipitant.

Similar to our second case, Achour et al.[10] reported a 19-year-old woman who developed AOSD following a COVID-19 diagnosis 8 weeks prior, whereas our second patient developed AOSD 2 weeks after the COVID-19 diagnosis. Although their patient exhibited significantly higher ferritin levels (>25,000 ng/dL) compared to our second case (12,189 ng/mL), their patient also showed improvement after receiving steroid treatment (prednisolone).

Historically, corticosteroids have been considered the first line of treatment for AOSD.[11] However, controlling the activity of the disease often requires high doses, which increase the risk of side effects. Therefore, recent recommendations suggest limiting the duration and frequency of steroid treatment. As an alternative, IL-1 blocking therapy can be initiated early in the course of the disease.[12] IL-6 blocking therapy is usually reserved for glucocorticoid-dependent or glucocorticoid-resistant AOSD cases, whereas methotrexate is recommended for treating arthritis associated with AOSD.[12]

In the case of our first patient, we had to use methotrexate and IL-1 blocking therapy with Anakinra to control the disease, as she had experienced side effects from corticosteroids on two previous occasions. For our second patient, we treated her with corticosteroids (prednisone), and she responded well without any side effects. However, her rheumatologist is considering starting IL-1 blocking therapy with Canakinumab as well.

Evidence suggests that COVID-19 could trigger AOSD flare-ups, even in children with juvenile idiopathic arthritis. An observational study by Naddei et al.[13] revealed a significant increase in disease flare-ups among patients with juvenile idiopathic arthritis during the COVID-19 pandemic compared to the preceding year. This finding strengthens the evidence of the potential association between COVID-19 and exacerbations of AOSD.

While the exact mechanism is not entirely understood, there are similarities in the inflammatory markers and cytokine profiles of both AOSD and COVID-19. This could indicate a shared underlying mechanism that explains why COVID-19 can lead to AOSD or worsen its symptoms. Further research is necessary to fully comprehend the intricate connections between the two conditions and their immunological effects.

Conclusions

Evidence suggests potential overlaps between AOSD and COVID-19. These two conditions share symptoms, inflammatory markers, and cytokine profiles, which may indicate similar underlying mechanisms. It has been observed that COVID-19 can precipitate the onset of AOSD or trigger flare-ups in adults and children with juvenile idiopathic arthritis. Therefore, clinicians should be aware of this possibility. Further research is needed to improve clinical management, outcomes, and enhance our understanding of both conditions.

Acknowledgements

None.

Authors contributions

SF-H and AJQA created the initial draft for the manuscript, performed the relevant literature review, and edited the revisions and final draft. GIL made revisions while creating the drafts and was the internist in charge of the care of the patients. SF-H, GIL, and AJQA participated in the writing of the manuscript. All authors contributed enough to claim authorship of the manuscript and approved the final versions of it.

Declaration of conflicting interests

The author) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

ORCID iD

Alejandro José Quiroz Alfaro https://orcid.org/0000-0002-7373-1192

References

1. Efthimiou P, Kontzias A, Hur P, et al. Adult-onset Still's disease in focus: clinical manifestations, diagnosis, treatment, and unmet needs in the era of targeted therapies. *Semin Arthritis Rheum* 2021; 51: 858–874.
2. Quiroz Alfaro AJ, Rodriguez Acosta IJ, Tanaka Takegami M, et al. *Chryseobacterium Indologenes* sepsis and acute renal failure secondary to abdominal compartment syndrome in a confirmed COVID-19 patient. *Case Rep Crit Care* 2022; 2022: 7946158.
3. Zebardast A, Hasanzadeh A, Ebrahimian Shiadeh SA, et al. COVID-19: a trigger of autoimmune diseases. *Cell Biol Int* 2023; 47: 848–858.

4. Kawasaki T, Ooka S, Mizushima M, et al. COVID-19 and adult-onset Still's disease as part of hyperferritinemic syndromes. *Mod Rheumatol Case Rep* 2022; 6: 101–105.
5. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992; 19: 424–430.
6. Wang MY, Jia JC, Yang CD, et al. Pathogenesis, disease course, and prognosis of adult-onset Still's disease: an update and review. *Chin Med J (Engl)* 2019; 132: 2856–2864.
7. Feist E, Mitrovic S and Fautrel B. Mechanisms, biomarkers and targets for adult-onset Still's disease. *Nat Rev Rheumatol* 2018; 14: 603–618.
8. Bamidis AD, Koehler P, di Cristanziano V, et al. First manifestation of adult-onset Still's disease after COVID-19. *Lancet Rheumatol* 2021; 3: e319–e321.
9. Gottschalk MN, Heiland M, Nahles S, et al. Increased incidence of adult-onset Still's disease in association with COVID-19 vaccination and SARS-CoV-2 infection. *Orphanet J Rare Dis* 2023; 18: 50. 20230310.
10. Achour TB, Elhaj WB, Jridi M, et al. Adult-onset Still's disease after SARS-Cov-2 infection. *Clin Case Rep* 2023; 11: e7006.
11. Jamilloux Y, Gerfaud-Valentin M, Henry T, et al. Treatment of adult-onset Still's disease: a review. *Ther Clin Risk Manag* 2015; 11: 33–43.
12. Leavis HL, van Daele PLA, Mulders-Manders C, et al. Management of adult-onset Still's disease: evidence- and consensus-based recommendations by experts. *Rheumatology (Oxford)* 2023: kead461.
13. Naddei R, Alfani R, Bove M, et al. Increased relapse rate during COVID-19 lockdown in an Italian cohort of children with juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2023; 75: 326–331.