Adult-onset Still's disease possibly consequent to asymptomatic COVID-19

Paula Ibáñez[1†], Ángel Manuel Iniesta[2], Ángel Robles[3], Mariana Gutiérrez[1], Francisco Bermúdez[1], Juan Carlos Martín[1†*]

European Journal of Medical Case Reports
Volume 5(7):218–221
https://doi.org/10.24911/ejmcr/173-1613255228

ABSTRACT

Background: In some patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease 2019 [COVID-19]), an uncontrolled release of inflammatory cytokines is characteristic. COVID-19 and adult-onset Still's disease (AOSD) have been included by some authors in the "hyperferritinemic syndromes." Another hyperinflammatory syndrome (with variable features of Kawasaki disease) called multisystem inflammatory syndrome (MIS) has been described in patients who have had SARS-CoV-2 infection.

Case Presentation: We present a previously healthy patient who developed hyperinflammatory reaction compatible with MIS; the clinical presentation is additionally compatible with AOSD, complicated with a mild myocarditis. The patient had a positive SARS-CoV-2 serology (immunoglobulins G and immunoglobulins M), but multiple reverse transcription-polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 on nasopharyngeal swab were negative or indeterminate, so we considered that it is possible that an asymptomatic SARS-CoV-2 infection could have been the trigger for Still's disease. 24 hours after starting methylprednisolone treatment, the fever was resolved and symptoms improved over the next few days, with persistent arthralgias.

Conclusion: Asymptomatic SARS-CoV-2 infection could trigger MIS with AOSD-like features.

Keywords: SARS-CoV-2, COVID-19, adult-onset Still's disease (AOSD), myocarditis, hyperferritinemic syndromes, multisystem inflammatory syndrome (MIS), multisystem inflammatory syndrome of children (MIS-C), case report.

Received: 13 February 2021 **Accepted:** 26 June 2021 **Type of Article:** CASE REPORT **Specialty:** Internal Medicine

Correspondence to: Juan Carlos Martín
*Servicio de medicina interna, Hospital universitario La Paz, Paseo de la Castellana, nº 261, 28046 Madrid, Spain.
Email: jcarlos.martin@salud.madrid.org
†Contributed equalitly
Full list of author information is available at the end of the article.

Background

In some patients with coronavirus disease 2019 (COVID-19), an uncontrolled release of inflammatory cytokines is characteristic [1,2]. COVID-19 has been included by some authors in the "hyperferritinemic syndromes" along with macrophage activation syndrome, adult-onset Still's disease (AOSD), catastrophic anti-phospholipid syndrome, and septic shock, due to clinical and laboratory similarities [3,4]. Hyperferritinemia could be a common pathogenic mediator of these syndromes generating a pro-inflammatory loop and triggering the "cytokine storm" [5].

Other inflammatory diseases, such us Kawasaki disease, have been described in the context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, often seen in the pediatric population [6,7]. A syndrome, called multisystem inflammatory syndrome (MIS) has become recognized, and it has been associated with previous infections by SARS-CoV-2 [8-11].

Case Presentation

A 42-years-old woman was admitted after 5 days of fever spikes (up to 39.2°C), chills, odynophagia, diarrhea (about 8 stools a day), mild dyspnea, asthenia, and a confluent centrifugal maculopapular rash that started on the trunk and spread to the extremities (Figure 1). 3 days before admission, two SARS-CoV-2 antigens (Ag) on nasopharyngeal swabs were negative. When she arrived, her heart rate was 107 beats per minute, blood pressure was 75/45 mm Hg, oxygen saturation was 98% on ambient air, and small jugular chain lymphadenopathies and hepatosplenomegaly were palpable. Pharyngitis was present. The rash was remitting.

The white cell count was 9,990/µl, with 9,340 neutrophils/µl and 370 lymphocytes/µl. She had alanine aminotransferase 78 U/l (0–35), aspartate aminotransferase 52 U/l (0–40), D-Dimer 4,310 ng/ml (0–500), Interleukin-6 (IL-6) 2.7 pg/ml (0–4.4), fibrinogen 1,047 mg/dl (150–450), C-reactive protein 257 mg/l (0–5), and ferritin 1,000 ng/ml (22–322). Multiple reverse transcription-polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 on nasopharyngeal swab were negative or indeterminate (on days 1, 3, 5, 6, 9, and 11 after admission). Throughout her hospitalization, she continued to have high fever,

pharyngeal pain, very significant asthenia, diarrhea, hypotension, and tachycardia; she developed strong shoulders and hips myalgias, along with wrists and interphalangeal arthralgias; lateral cervical lymphadenopathy was palpated, slight hepatomegaly and splenomegaly were palpable, and a macular rash persisted on the hands (Figure 2).

Antinuclear antibodies and rheumatoid factor were negative. Serologic tests for atypical pneumonia-producing bacteria, syphilis, toxoplasmosis, acute infection for rubeola, cytomegalovirus, parvovirus B19, Epstein–Barr virus, human immunodeficiency virus, and measles virus were negative; antibodies immunoglobulin G (IgG) and immunoglobulin M (IgM) using enzyme immunoassay against SARS-CoV-2 were positive. Polymerase chain reaction (PCR) testing for enteroviruses in blood was negative. A computer tomographic angiography did not show findings of pulmonary thromboembolism, but it showed a small consolidation in the parenchyma of the left lower lobe. Piperacillin/tazobactam was prescribed.

A transthoracic echocardiogram was carried out revealing signs suggestive of myocarditis: global hypokinesia and mild dysfunction of both ventricles (left ventricular ejection fraction of 48%, moderate functional mitral regurgitation, and mild-to-moderate tricuspid regurgitation). High-sensitivity troponin I was 52.9 ng/l (0–34.1) and B-type natriuretic peptide was 5,825 pg/ml (0–125).

On day 5 from her admission, it was considered that she met the criteria for adult-onset Still's disease with a mild myocarditis, and methylprednisolone 60 mg/day was prescribed, non-steroidal anti-inflammatory drugs, and carvedilol. After first dose of methylprednisolone, the fever resolved and her asthenia and general condition began to improve; only mild myalgias and arthralgias remained. Upon discharge, she had persistent arthralgias. A cardiac magnetic resonance imaging carried out 2 weeks after admission showed recovered ventricular ejection fraction, no significant valve disease, and slightly elevated values in the T1 and T2 image mapping sequences, suggesting inflammatory changes. At outpatient follow-up at 3 weeks, she remained afebrile, but arthralgias persisted in some joints including hands, wrists, elbows, feet, and ankles. Unfortunately, arthralgia delayed the tapering of corticosteroids and we are currently considering other possible therapies.

The patient lives with her husband and two daughters, one 6 years old and the other 8 months old; all were asymptomatic when the patient was admitted but, given her clinical picture and positive SARS-CoV-2, family members were tested at another medical center to rule out SARS-CoV-2 infection. Her husband had positive antibodies for SARS-CoV-2 IgG, titer 2.74 (>1.1; positive) with negative IgM, titer 0.48 (<0.9; negative). However, the two daughters had negative SARS-CoV-2 PCR. 1 month later, the oldest daughter had positive IgM, titer 2.61 (>1.1; positive), and negative IgG, titer 0.21 (<0.9; negative), serology; with negative RT-PCR. The younger daughter had positive IgG and negative IgM (titer not available).

Discussion

Cytokine storm in patients with COVID-19 may induce a variety of clinical manifestations relating to a multisystem inflammatory process, such us acute respiratory distress syndrome, macrophage activation syndrome (hemophagocytic lymphohistiocytosis), atypical Kawasaki disease, or toxic shock [5-7].

A syndrome called MIS, characterized by fever, multiple organ system involvement with shock and cardiac injury, gastrointestinal symptoms, and markedly elevated inflammatory biomarkers, has become recognized, and it has been associated with previous infections by SARS-CoV-2 [8–11]. The patient we describe had features of MIS, and also of an AOSD like syndrome [12]. After an extended research, we have found only two cases describing AOSD after SARS-CoV-2 infection [13,14]. As in one of the cases, our patient was thought to have SARS-CoV-2 infection based on serology [13]. In our patient, no other triggering process for AOSD was found. In the other case,

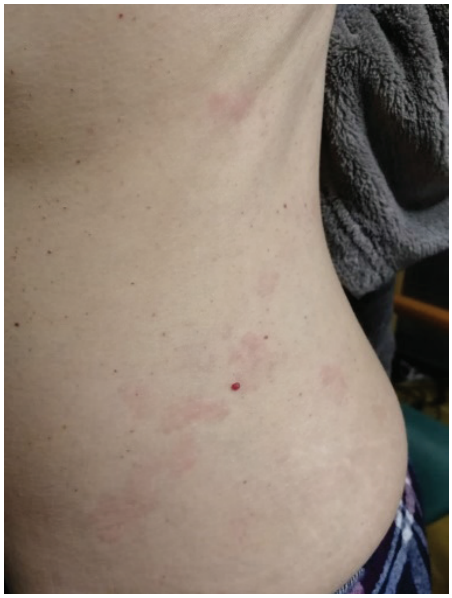

Figure 1. *Confluent maculopapular rash over the trunk.*

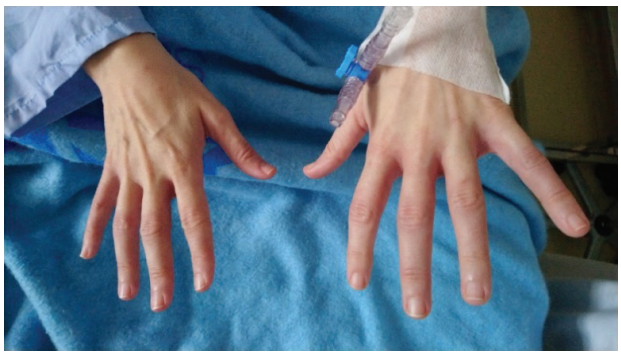

Figure 2. *Macular rash on hands.*

the patient developed signs of SARS-CoV-2 infection, with long-term sequelae of COVID-19 during 6 months, and when she developed pericarditis with pericardial effusion, AOSD was diagnosed [14].

Cases of MIS after COVID-19 in children are described in the literature, such as Kawasaki disease; these inflammatory processes share some characteristics with AOSD. DeBiasi et al. [7] describe one 4-year-old boy with features consistent with the multisystem inflammatory syndrome of children (MIS-C) with Kawasaki disease shock-like presentation including hyperinflammatory state, hypotension, profound myocardial depression, and COVID-19. There is one report of a 16-year-old patient with COVID-19 who had MIS-C with global multisystem organ dysfunction [7]. Riphagen et al. [6] describe one series of children with hyperinflammatory shock during COVID-19 pandemic, some of them with myocardial damage; some of these patients were SARS-CoV-2 positive or were SARS-CoV-2 negative, but had been exposed to COVID-19 patients.

An article has recently been published that describes 11 young adult patients with acute or fulminant myocarditis along with COVID-19, and postinfectious MIS [8]. Nine of these patients had positive serology for SARS-CoV-2, with negative RT-PCR testing, which suggested that SARS-CoV-2 infection had occurred several weeks prior, followed by a postinfectious inflammatory syndrome.

It has been considered a significant heterogeneity in the human immune response to SARS-CoV-2 with the spectrum of SARS-CoV-2-associated clinical inflammatory syndromes identified in adult and pediatric populations [15].

We intend to demonstrate with this case, some clinical similarities between MIS and AOSD, and the possible consequences of the SARS-CoV-2 infection (COVID-19). Immune response to this virus can lead to heart disease such as myocarditis and other acute cardiac manifestations [16,17].

Conclusion

SARS-CoV-2 infection can trigger uncommon inflammatory responses such as MIS or AOSD. Further investigation is needed to determine the immunological and/or genetic spectrum that underlies the inflammatory complications of SARS-CoV-2.

What is new?

In some patients with SARS-CoV-2 infection, an uncontrolled release of inflammatory cytokines is characteristic. SARS-CoV-2 infection could trigger adult-onset Still's disease.

List of Abbreviations

AOSD	Adult-onset Still's disease
COVID-19	Coronavirus disease 2019
IgG	Immunoglobulin G
IgM	Immunoglobulin M
MIS	Multisystem inflammatory syndrome
MIS-C	Multisystem inflammatory syndrome of children
RT-PCR	Reverse transcription-polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this case report.

Funding

None.

Consent for publication

Written informed consent was taken from the patient.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

Author details

Paula Ibáñez[1], Ángel Manuel Iniesta[2], Ángel Robles[3], Mariana Gutiérrez[1], Francisco Bermúdez[1], Juan Carlos Martín[1]

1. Servicio de medicina interna, Hospital universitario La Paz, Paseo de la Castellana, nº 261, 28046 Madrid, Spain
2. Servicio de cardiología, Hospital universitario La Paz, Paseo de la Castellana, nº 261, 28046 Madrid, Spain
3. Unidad de enfermedades autoinmunes, servicio de medicina interna, Hospital universitario La Paz, Paseo de la Castellana, nº 261, 28046 Madrid, Spain

References

1. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020;39(7):2085–94. https://doi.org/10.1007/s10067-020-05190-5
2. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the "Cytokine Storm" in COVID-19. J Infect. 2020;80(6):607-13. https://doi.org/10.1016/j.jinf.2020.03.037
3. 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. https://doi.org/10.1016/j.autrev.2020.102573
4. Talotta R, Robertson E. Autoimmunity as the comet tail of COVID-19 pandemic. World J Clin Cases. 2020;8(17):3621–44. https://doi.org/10.12998/wjcc.v8.i17.3621
5. Ruscitti P, Berardicurti O, Di Benedetto P, Cipriani P, Iagnocco A, Shoenfeld Y, et al. Severe COVID-19, another piece in the puzzle of the hyperferritinemic syndrome. An immunomodulatory perspective to alleviate the storm. Front Immunol. 2020;11:1130. https://doi.org/10.3389/fimmu.2020.01130
6. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395(10237):1607–8. https://doi.org/10.1016/S0140-6736(20)31094-1
7. DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, et al. Severe coronavirus disease-2019 in children and young adults in the Washington, DC, Metropolitan Region. J Pediatr. 2020;223:199–203.e1. https://doi.org/10.1016/j.jpeds.2020.05.007

8. Hékimian G, Kerneis M, Zeitouni M, Cohen-Aubart F, Chommeloux J, Bréchot N, et al. Coronavirus disease 2019 acute myocarditis and multisystem inflammatory syndrome in adult intensive and cardiac care units. Chest. 2021;159(2):657–62. Available from: https://www.sciencedirect.com/science/article/pii/S0012369220343592. https://doi.org/10.1016/j.chest.2020.08.2099
9. Tenforde MW, Morris SB. Multisystem inflammatory syndrome in adults: coming into focus. Chest. 2021;159(2):471-2. https://www.sciencedirect.com/science/article/pii/S0012369220345190. https://doi.org/10.1016/j.chest.2020.09.097
10. Vogel TP, Top KA, Karatzios C, Hilmers DC, Tapia LI, Moceri P, et al. Multisystem inflammatory syndrome in children and adults (MIS-C/A): case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2021;39(22):3037–49. https://doi.org/10.1016/j.vaccine.2021.01.054
11. Moghadam P, Blum L, Ahouach B, Radjou A, Lambert C, Scanvic A, et al. Multisystem inflammatory syndrome with particular cutaneous lesions related to COVID-19 in a young adult. Am J Med. 2021;134(1):e36–7. https://doi.org/10.1016/j.amjmed.2020.06.025
12. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. Autoimmun Rev. 2014;13(7):708–22. https://doi.org/10.1016/j.autrev.2014.01.058
13. de Carvalho JF. COVID-19 in Still's disease. Eur Rev Med Pharmacol Sci. 2020;24(24):12627–9. https://doi.org/10.26355/eurrev_202012_24158
14. Bamidis AD, Koehler P, di Cristanziano V, Rasche K, Demirel B, Bacher P, et al. First manifestation of adult-onset Still's disease after COVID-19. Lancet Rheumatol. 2021;3(5):e319–21. https://doi.org/10.1016/S2665-9913(21)00072-2
15. Weatherhead JE, Clark E, Vogel TP, Atmar RL, Kulkarni PA. Inflammatory syndromes associated with SARS-CoV-2 infection: dysregulation of the immune response across the age spectrum. J Clin Invest. 2020;130(12):6194–7. https://doi.org/10.1172/JCI145301
16. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142:429–36. https://doi.org/10.1161/CIRCULATIONAHA.120.048360
17. Siripanthong B, Nazarian S, Muser D, Deo R, Santangeli P, Khanji MY, et al. Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm. 2020;17(9):1463–71. https://doi.org/10.1016/j.hrthm.2020.05.001

Summary of the case

1	**Patient (gender, age)**	Female, 42-year-old
2	**Final diagnosis**	AOSD after SARS-CoV-2 infection complicated with a mild myocarditis
3	**Symptoms**	Fever spikes (up to 39.2°C), chills, odynophagia, diarrhea, rash over the trunk and extremities, myalgias, and arthralgias
4	**Medications**	Methylprednisolone and carvedilol
5	**Clinical procedure**	Computer tomographic angiography, transthoracic echocardiogram, and cardiac magnetic resonance
6	**Specialty**	Internal Medicine, Infectious Diseases