



ELSEVIER

Contents lists available at ScienceDirect

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Case Report

Cardiac involvement in Adult Multisystemic Inflammatory Syndrome related to COVID-19. Two case reports



Sergio Carrasco-Molina (MD)^{a,*}, Luis Ramos-Ruperto (MD)^a, Paula Ibáñez-Mendoza (MD)^a, Juan Carlos Martín-Gutiérrez (MD, PhD)^a, Elena Ruíz-Bravo (MD)^b, Ángel Manuel Iniesta-Manjavacas (MD)^c, Elsa Prieto-Moriche (MD)^c, Ángel Robles-Marhuenda (MD)^d

^a Internal Medicine Department, Hospital Universitario La Paz, Madrid, Spain

^b Pathology Department, Hospital Universitario La Paz, Madrid, Spain

^c Cardiology Department, Hospital Universitario La Paz, Madrid, Spain

^d Autoimmune Diseases Unit, Hospital Universitario La Paz, Madrid, Spain

ARTICLE INFO

Article history:

Received 23 October 2021

Revised 11 January 2022

Accepted 28 January 2022

Keywords:

Multisystemic inflammatory syndrome in adults

Severe acute respiratory syndrome-coronavirus-2

Coronavirus disease 2019

Myocarditis

Corticosteroids

ABSTRACT

In this article we describe two cases that presented with persistent fever and a hyperinflammatory state in association with severe acute respiratory syndrome-coronavirus-2 infection with various negative reverse transcription-polymerase chain reaction results. These cases subsequently developed myocarditis with cardiogenic shock that required vasoactive drugs and had a good response to corticosteroid treatment. All cases met criteria for a definitive case of multisystemic inflammatory syndrome in adults, a recently described entity associated with coronavirus disease 2019, which has a good response to immunomodulators and a good prognosis in most cases.

<Learning objective: Multisystemic inflammatory syndrome in adults is a severe disease with predominantly cardiac involvement, associated with severe acute respiratory syndrome-coronavirus-2 infection. The presentation of these two cases shows the importance of early recognition, especially in this coronavirus 2019 pandemic scenario in which almost anyone is susceptible to have had contact with the virus. It usually has a good therapeutic response to corticosteroids and invasive diagnostic tests, such as endomyocardial biopsy, could be avoided.>

© 2022 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

In January 2020, a new virus (severe acute respiratory syndrome-coronavirus-2; SARS-CoV-2) appeared in Wuhan City, China, later spreading around the world and causing the pandemic that we continue to experience [1]. Initially, we could find in literature descriptions of organic damage directly caused by SARS-CoV-2, predominantly pulmonary involvement [2]. However, it has been observed that certain predisposed patients can develop a hyperinflammatory immune response caused by an excessive reaction to the virus, leading to extrapulmonary affections. These responses have been described in an early stage (less than 14 days after infection) and also as late reactions (more than 14 days after infection) [3]. Here we present the report of three adults that developed a late inflammatory response after SARS-CoV-2 infection

compatible with multisystemic inflammatory syndrome (MIS) with significant cardiovascular involvement.

Case 1

The first case is a 46-year-old man, with a history of SARS-CoV-2 infection four weeks earlier, consulted in emergency room due to daily fever up to 39°C for 7 days and a macular rash on the trunk (Fig. 1A). No clear foci were evident in anamnesis, physical examination was normal except for the fever and macular rash. Laboratory tests showed a predominant inflammatory pattern: C-reactive protein 300 mg/l (<5 mg/l), ferritin 1579 ng/ml (<10–291 ng/ml), and procalcitonin 1 ng/mg (<0.5 ng/mg). Blood and urine cultures were sterile. A reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 was negative, serology showed past infection for toxoplasmosis, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19. Also, no acute nor chronic infection was evident for syphilis, hepatotropic virus, human immunodeficiency virus (HIV),

* Corresponding author at: Sergio Carrasco-Molina MD, Plaza de la Castellana, 261, 28046, Madrid, Spain.

E-mail address: scarrascom@salud.madrid.org (S. Carrasco-Molina).

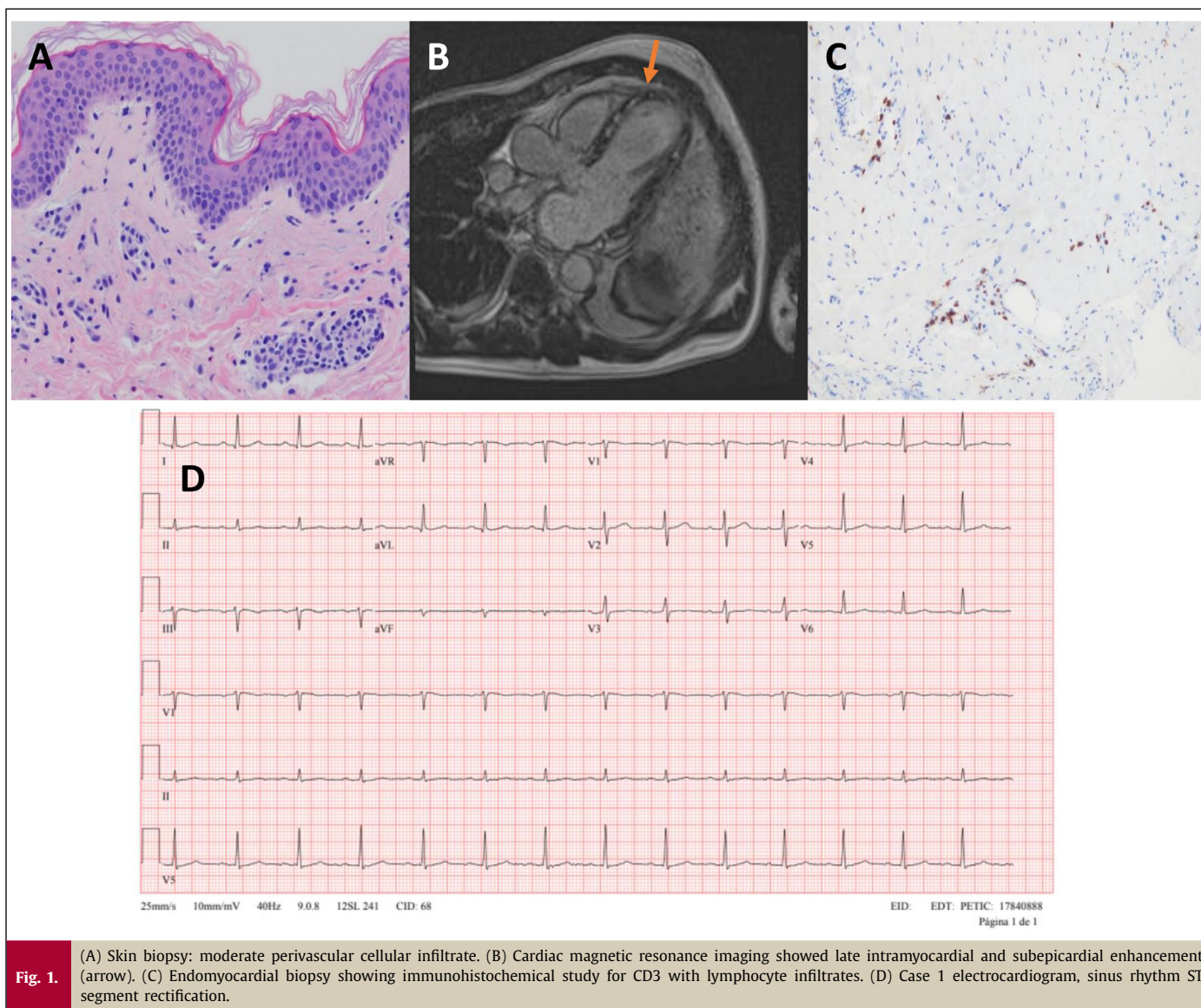


Fig. 1.

(A) Skin biopsy: moderate perivascular cellular infiltrate. (B) Cardiac magnetic resonance imaging showed late intramyocardial and subepicardial enhancement (arrow). (C) Endomyocardial biopsy showing immunohistochemical study for CD3 with lymphocyte infiltrates. (D) Case 1 electrocardiogram, sinus rhythm ST segment rectification.

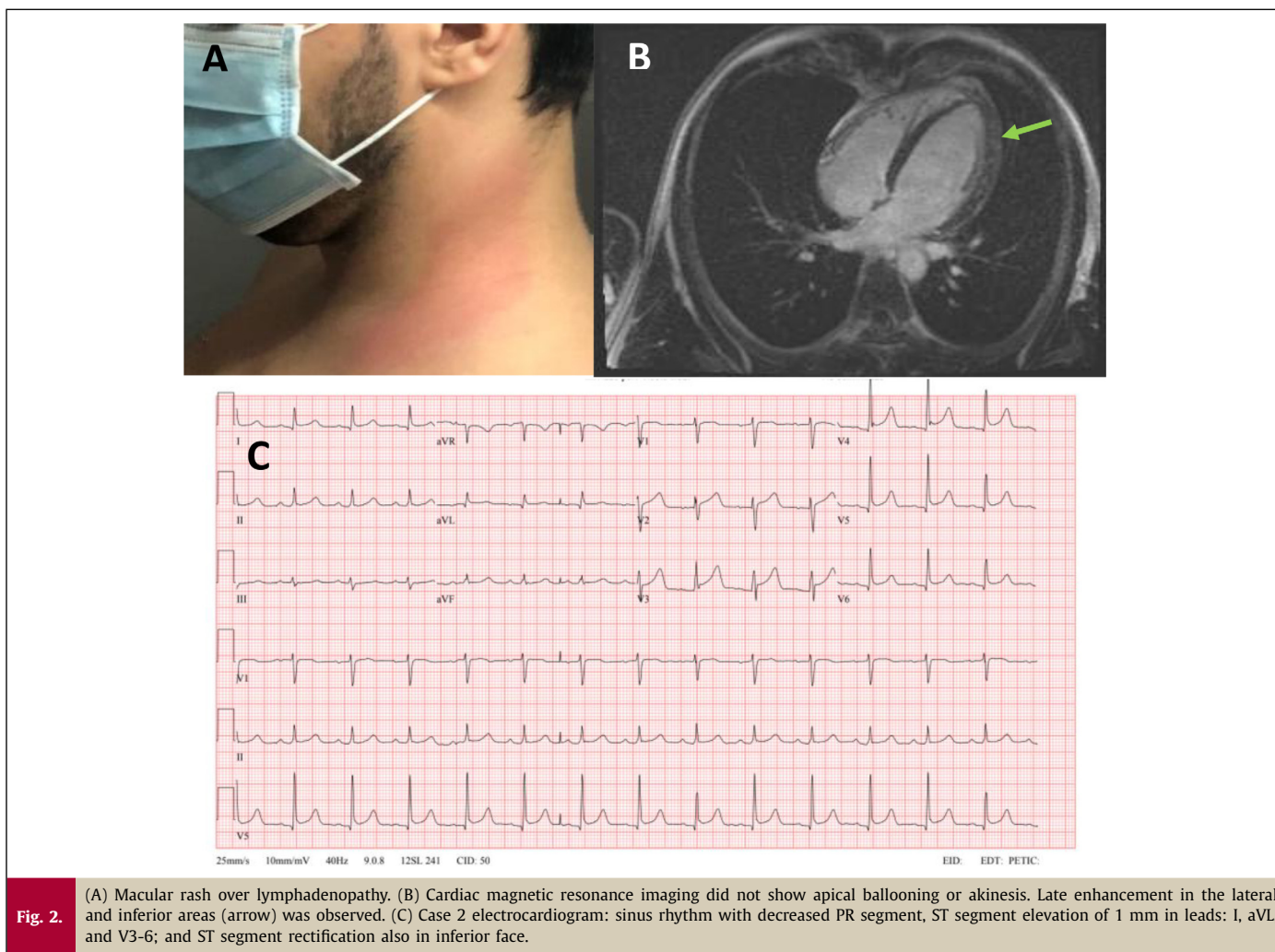
Chlamydia pneumoniae, *Mycoplasma pneumoniae*, and *Coxiella burnetii*. Also, autoantibodies were negative including antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), and anti-extracellular antibodies panel (Ro, La, Sm, RNP, Scl-70 and Jo-1). Immunoglobulin (Ig)G, IgA, and IgM levels were normal, and no complement consumption was detected.

During admission, he presented with dyspnea and oppressive central thoracic pain with significant impairment of general condition, hypotension, and peripheral oxygen saturation of 90% without oxygen supplementation. Compared to previous electrocardiograms, a diffuse ST segment rectification was observed (Fig. 1D). Analysis showed a maintained inflammatory pattern and high-sensitivity troponin I was 19356 ng/l (<34.1). A transthoracic echocardiogram showed a lower mid-apical akinesia and hypokinesia in basal and middle septum and lower basal face, with a left ventricular ejection fraction (LVEF) of 30%. He was admitted to the coronary care unit due to cardiogenic shock and vasoactive drugs were required. Suspecting myocarditis, boluses of methylprednisolone 500 mg were started for 3 days followed by oral methylprednisolone 1 mg/kg/day, with improvement in myocardial function and decline in inflammatory parameters. Computed tomography of the coronary arteries showed no sig-

nificant lesions, and cardiac magnetic resonance imaging (MRI) showed evidence of myocardial inflammation (Fig. 1B). An endomyocardial biopsy revealed a lymphocytic inflammatory infiltrate (35 CD3+/mm² lymphocytes), without myocyte necrosis or fibrosis (Fig. 1C). Immunohistochemical study for SARS-CoV-2 did not detect the presence of the virus. After clinical improvement, the patient was discharged with decreasing doses of corticosteroids and azathioprine and no recurrence has been evident in 3 months' follow-up. At 3 months after discharge, the patient had an LVEF of 64.9% verified by echocardiography and the patient was asymptomatic.

Case 2

The second case is a 37-year-old man who came to the hospital with high fever up to 39.3°C, predominantly in the afternoon. He had a left cervical painful lump,odynophagia, and rash (Fig. 2A). He had been diagnosed with SARS-CoV-2 infection by RT-PCR and pneumonia 16 days before the beginning of the fever. The rest of the physical examination showed no relevant findings. Laboratory tests showed an inflammatory pattern: C-reactive protein 380 mg/l (normal <5), ferritin 1591 ng/ml (10-291), and procalc-



tonin 0.9 ng/ml (<0.5). Blood and urine cultures were sterile. A RT-PCR for SARS-CoV-2 was negative, serology showed past infection for toxoplasmosis, CMV, EBV, and parvovirus B19. Also, no acute nor chronic infection was evident for syphilis, hepatotropic virus, HIV, *C. pneumoniae*, *M. pneumoniae*, and *C. burnetti*. Also, autoantibodies were negative including ANA, ANCA, and anti-extranuclear antibodies panel. IgG, IgA, and IgM levels were normal, and no complement consumption was detected. During his admission, the patient presented with hypotension without chest pain, requiring noradrenaline to maintain blood pressure. High-sensitivity troponin I was 3549 ng/l (<34.1); and inflammatory pattern was maintained in blood test. N-terminal prohormone B-type natriuretic peptide was 2767 pg/mL. The electrocardiogram showed sinus rhythm with decreased PR segment, ST segment elevation of 1 mm in leads: I, aVL, and V3-6; and ST segment rectification also in inferior face (Fig. 2C). A transthoracic echocardiogram was carried out with severe LVEF (28%) with global hypokinesia. Treatment was started with boluses of methylprednisolone 1 g per day for 3 days, continuing with corticoids descending pattern. The cardiac MRI was suggestive of myocardial inflammation (Fig. 2B). The patient evolved favorably during admission with recovery of ventricular function, with an LVEF of 43.7% verified by echocardiogram before hospital discharge. He went to his home with a descending corticoid regimen. At follow-up 3 months after hospital discharge he presented an LVEF of 56% verified by echocardiogram.

Discussion

MIS in adults (MIS-A) is characterized by fever, severe illness, and involvement of two or more organ systems, especially cardiac affection, combined with laboratory evidence of inflammation and laboratory or epidemiologic evidence of SARS-CoV-2 infection. As said, it was initially described in children and adolescents and recently it has been described in adults and diagnostic criteria have been proposed by the US Centers for Disease Control and Prevention [4]. Other classificatory criteria with different levels of evidence for MIS-A have subsequently been described [5]. The chronology with SARS-CoV2 infection has not been totally established: it seems that MIS-A develops in people who had suffered COVID19 with mild symptoms and not had serious pulmonary involvement. The time from infection to the onset of MIS-A symptoms is not clear: onset of MIS-A symptoms has been reported from days to several weeks after SARS-CoV2 infection, as in case 1 [6].

The molecular mechanisms that lead to hyperinflammation in MIS-A are largely unknown and limited to phenotypic characterizations. It is believed that the development of antibodies to SARS-CoV-2 may play a role, and may secondarily trigger macrophage activation leading to the clinical picture. This suggests that symptomatic or asymptomatic SARS-CoV-2 infection would be followed a few weeks later by a hyperinflammatory response and immune-mediated systemic and cardiac damage after anti-

body development, demonstrated by a combination of positive serological results on admission with negative or mildly positive RT-PCR [5–7].

Endomyocardial biopsies of these patients showed mild inflammatory myocarditis (lymphocytic or macrocytic infiltrate) with no evidence of direct viral infection in cardiomyocytes, as in case 1 [8]. If we use classificatory criteria of MIS in children and adults, our two cases presented in this article meet level 1 of diagnostic certainty and can be defined as definitive cases of MIS-A.

As for treatment, there are no generalized recommendations at the present time, although the focus is on supportive treatment of cardiogenic shock in a coronary unit/intensive care unit. The response to corticosteroids is good in almost all cases described, and intravenous boluses can be used. Other treatments have been tried in patients who do not respond to corticosteroids, including immunoglobulins, anakinra, and tocilizumab [9].

In summary, MIS-A is a recently described severe disease with predominantly cardiac involvement, associated with late infection or exposure to SARS-CoV-2. The presentation of these two cases shows the importance of early recognition, especially in this COVID19 pandemic scenario in which almost anyone is susceptible to have contact with the virus. It usually has a good therapeutic response to corticosteroids and immunosuppressants and invasive diagnostic tests, such as endomyocardial biopsy, could be saved.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None of the authors have any conflicts of interest to declare.

References

- [1] Li H, Liu Z, Ge J. Scientific research progress of COVID-19/SARS-CoV-2 in the first five months. *J Cell Mol Med* 2020;24:6558–70.
- [2] Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents* 2020;55:105924.
- [3] Ramos-Casals M, Brito-Zerón P, Mariette X. Systemic and organ-specific immune-related manifestations of COVID-19. *Nat Rev Rheumatol* 2021;17:315–32.
- [4] Morris SB. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection – United Kingdom and United States, March–August 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1450–6. Available from: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6940e1.html>.
- [5] Vogel TP, Top KA, Karatzios C, Hilmers DC, Tapia LI, Mocerri P, Giovannini-Chami L, Wood N, Chandler RE, Klein NP, Schlaudecker EP, Poli MC, Muscal E, Munoz FM. 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;39:3037–49.
- [6] Hékimian G, Kerneis M, Zeitouni M, Cohen-Aubart F, Chommeloux J, Bréchet N, Mathian A, Lebreton G, Schmidt M, Hié M, Silvain J, Pineton de Chambrun M, Haroche J, Burrel S, Marot S, et al. Coronavirus disease 2019 acute myocarditis and multisystem inflammatory syndrome in adult intensive and cardiac care units. *Chest* 2021;159:657–62.
- [7] 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;130:6194–7.
- [8] Most ZM, Hendren N, Drazner MH, Perl TM. Striking similarities of multisystem inflammatory syndrome in children and a myocarditis-like syndrome in adults: overlapping manifestations of COVID-19. *Circulation* 2021;143:4–6.
- [9] Cattaneo P, Volpe A, Cardellino CS, Riccardi N, Bertoli G, Ursini T, Ustalli A, Lodi G, Daroui I, Angheben A. Multisystem inflammatory syndrome in an adult (MIS-A) successfully treated with anakinra and glucocorticoids. *Microorganisms* 2021;9:1393.