Severe Multisystem Inflammatory Syndrome Associated With SARS-CoV-2 in a 31-Year-Old Male Patient: The First Clinical Case Report From the Republic of Cyprus

Despina Markoulaki 1, Stelios Iordanou 1, Demetris Koukios 1, Ioanna Christoldoulou 1, Panos Papadopoulos 1, Chrystalla Timiliotou-Matsentidou 1

1. Intensive Care Unit, Limassol General Hospital, Limassol, CYP

Corresponding author: Stelios Iordanou, iordanou.stelios@gmail.com

Abstract

Multisystem inflammatory syndrome (MIS) in adults associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is increasingly reported in published literature, although published reports remain sparse. In this report, we describe our first experience with a 31-year-old Caucasian male who developed severe MIS 31 days after a mild SARS-CoV-2 infection. The patient developed fever, elevated C-reactive protein (CRP), procalcitonin (PCT), reduced ejection fraction (EF), and shock. After extensive diagnostic work-up, nothing was found to justify his shock manifestation. A similar treatment to MIS in children (MIS-C) with immunoglobulins, corticosteroids, and anticoagulants led to a remarkable clinical improvement.

MIS in adults (MIS-A) can be fatal. The early identification of MIS plays a crucial role in the prompt initiation of suitable treatment. Therefore, differential diagnosis and exclusion of other causes of illness are of priority. We believe that MIS in children treatment guidelines can be reformed in a way to include MIS in adults as well.

Introduction

An increasing number of studies in published literature reports multisystem inflammatory syndrome (MIS) in children (MIS-C), associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Reports from Europe and North America have described instances with symptoms resembling Kawasaki syndrome, toxic shock, and MIS manifestations [1]. Treatment included mainly immunoglobulin and steroids [1]. At the same time, there has been an increasing number of reports in young adults [2] similar to that initially described in children [3,4].

Before October 2021, the case definition for MIS in adults (MIS-A) was not available. According to the recently published CDC (Centers for Disease Control) definition for MIS-A, the patient must be over 21 years of age, hospitalized for 24 hours, or with an illness resulting in death, which meets specific clinical and laboratory criteria, and in the absence of alternative diagnosis for the illness such as bacterial sepsis or exacerbation of a chronic medical condition [5]. Despite the recently published MIS-A definition, treatment recommendations are not yet available; therefore, in the majority of reports, the patients were treated according to the MIS-C recommendations.

From December 31, 2019, to late November 2021, 129,158 cases of SARS-CoV-2 have been reported in the Republic of Cyprus [6], including 589 deaths. To our knowledge, this is the first case in the Republic of Cyprus involving MIS associated with SARS-CoV-2 in an adult patient similar to that described in children [7].

Case Presentation

The case refers to a 31-year-old Caucasian male with a COVID-19 infection confirmed by reverse transcription-polymerase chain reaction (RT-PCR) of a specimen collected with a nasopharyngeal swab on February 12, 2021. His initial symptoms included mild fever and malaise. After an uneventful initial recovery, 31 days after his initial positive PCR test, the patient developed a sudden high fever, malaise, and difficulty breathing, which led him to seek medical attention.

The patient visited a private hospital with tachycardia of 140 beats per minute, pyrexia of 39.6°C, oxygen saturation of 90% (on ambient air), and a blood pressure of 70 over 45 mmHg. He was given 2 g ceftriaxone
IV and then was immediately transferred to the Limassol General Hospital, Limassol, Cyprus, where he was admitted to the ICU.

On admission, the patient was fully oriented but restless. He exhibited tachypnoea (30-45 RR per min). On a non-rebreathing mask at 15 l/min, arterial blood gases revealed a PO$_2$ of 62 mmHg, PCO$_2$ of 32 mmHg, pH of 7.39, and lactate levels less than 2 mmol/L. His chest x-rays were unremarkable in terms of infiltrates (Figure 1). Blood pressure on admission was 80/40 (mean arterial pressure [MAP]: 58) mmHg. Given this hemodynamic profile, vasopressor (noradrenaline) support was required and continued for several days. The maximum dose of noradrenaline was used on days two and three (0.1 mcg/kg/min) and stopped on day seven.

**FIGURE 1: Chest x-rays**

(a) Admission day, (b) day two, (c) day five, and (d) day eight.

Physical examination revealed conjunctivitis, lip cheilitis, and diffuse rash on his palms and lower extremities (Figure 2).
The results of laboratory tests upon admission showed an elevated C-reactive protein (CRP) of 372.46 mg/L (<5), a lymphocyte count of $0.78 \times 10^3/\mu L (1-3.4)$, white blood cells (WBC) of $14.6 \times 10^3/\mu L (3.6-9.2)$, a troponin of 0.75 ng/mL (0 and 0.04), creatinine of 2.44 mg/dL (0.67-1.17), urea of 111 mg/dL (17-43), and procalcitonin (PCT) of 10 µg/L (<2) (Table 1). Specimens were collected according to the European Centre for Disease Prevention and Control (ECDC) guidance and included a nasopharyngeal swab for SARS-CoV-2. The patient had no previous medical history and no known comorbidities. His ECG was unremarkable, and a transthoracic echocardiogram displayed a mild to moderately reduced ejection fraction (EF) of 50%-55% with a trace of pericardial effusion. A full-body contrast-enhanced CT revealed cervical and mesothorax lymphadenopathy and bronchiectasis without infiltrates.
| Laboratory | Day one | Day two | Day three | Day four | Day five | Day six | Day seven | Day eight | Day nine |
|------------|---------|---------|-----------|----------|----------|---------|-----------|----------|---------|
| WBC 10^3/μL | 14.62   | 22.11   | 22.62     | 17.25    | 7.66     | 4.61    | 6.55      | 5.16     | 8.84    |
| NEUT%      | 91.8    | 95.2    | 90.2      | 89.6     | 86.3     | 83.1    | 86.5      | 84.7     | 89.2    |
| LYM%       | 5.3     | 3.1     | 4.8       | 6.6      | 9.3      | 11.5    | 6.9       | 8.7      | 6.9     |
| MONO%      | 1.5     | 1.2     | 2.7       | 2        | 3.3      | 4.3     | 5.3       | 5.4      | 2.4     |
| EOS%       | 0.1     | 0.1     | 0.4       | 0.1      | 0        | 0       | 0         | 0        | 0.6     |
| BASO%      | 0.1     | 0.2     | 0.2       | 0.2      | 0.1      | 0       | 0         | 0        | 0.1     |
| IG%        | 0.30    | 0.20    | 1.7       | 1.3      | 1        | 1.10    | 1.10      | 1.2      | 0.8     |
| NEUT 10^3/μL | 13.42  | 21.03   | 20.43     | 15.46    | 6.61     | 3.83    | 5.67      | 4.37     | 7.89    |
| LYM 10^3/μL | 0.78    | 0.69    | 1.08      | 1.17     | 0.71     | 0.53    | 0.45      | 0.45     | 0.61    |
| MONO 10^3/μL | 0.22   | 0.26    | 0.6       | 0.34     | 0.25     | 0.2     | 0.35      | 0.28     | 0.21    |
| EOS 10^3/μL | 0.14    | 0.03    | 0.08      | 0.02     | 0        | 0       | 0         | 0        | 0.05    |
| BASO 10^3/μL | 0.01   | 0.05    | 0.05      | 0.04     | 0.01     | 0       | 0.01      | 0        | 0.01    |
| IG 10^3/μL  | 0.05    | 0.05    | 0.38      | 0.22     | 0.08     | 0.05    | 0.07      | 0.06     | 0.07    |
| RBC 10^3/μL | 4.62    | 44.4    | 4.33      | 4.18     | 3.74     | 3.38    | 3.52      | 3.61     | 3.85    |
| HGB g/dL    | 12.8    | 12.6    | 12.3      | 11.6     | 10.5     | 9.6     | 9.8       | 10       | 10.9    |
| HCT%        | 39.6    | 38      | 37.5      | 36.0     | 32.4     | 30.2    | 31.1      | 31.7     | 33.5    |
| MCV fL      | 85.7    | 85.6    | 86.6      | 86.1     | 86.6     | 89.3    | 88.4      | 87.8     | 87      |
| MCH pg      | 27.7    | 28.4    | 26.4      | 27.8     | 28.1     | 28.4    | 27.8      | 27.7     | 28.3    |
| PLT 10^3/μL | 136     | 172     | 157       | 199      | 175      | 163     | 173       | 156      | 177     |
| MPV fL      | 11.3    | 11.5    | 11.9      | 11.7     | 11.8     | 11.3    | 11.3      | 11       | 11      |
| CRP mg/L    | 372.46  | 423.9   | 350.1     | 230      | 121      | 73.36   | 47        | 31.8     | 22.13   |
| PCT ng/m    | >10     |         |           |          |          |         |           |          | 2       |
| LDH         | 445     | 453     | 615       | 613      | 473      | 465     | 513       | 498      |         |
| Urea mg/dL  | 111     | 73      | 66        | 71       | 106      | 111     | 95        | 86       | 86      |
| Creatinine  | 2.44    | 1.65    | 1.77      | 1.86     | 1.6      | 1.24    | 0.96      | 0.63     | 0.63    |
| Ferritin ng/ml | 3420  | 8060    | 6285      | 5503     | 3563     | 2815    |           |          |         |
| Troponin    | 0.75    | 0.87    | 0.08      | 0.08     |          |         |           |          |         |

**TABLE 1: Laboratory results**

WBC: White blood cells; NEUT: Neutrophils; LYM: Lymphocytes; MONO: Monocytes; EOS: Eosinophils; BASO: Basophils; IG: Immature granulocytes;
RBC: Red blood cells; HGB: Hemoglobin; HCT: Hematocrit; MCV: Mean corpuscular volume; MCH: Mean cell hemoglobin; PLT: Platelets; MPV: Mean platelet volume; LDH: Lactate dehydrogenase; CRP: C-reactive protein; PCT: Procalcitonin.

On day 2, the patient turned into a prone position with no result in oxygenation (PO2/FiO2 ratio of 68 on non-rebreather mask [NRM] 100%/15 litO2). The patient was intubated and mechanically ventilated due to severe persistent tachypnoea and hypoxia (PO2/FiO2 ratio of 114 on FiO2 1.00). That day’s laboratory tests revealed ferritin of 3420 ng/ml (peak on day 4: 8060 ng/ml) and an elevation of WBC to 22.11 x 10^3/μL (peak on day 3: 22.62 x 10^3/μL) (Tables 1, 2).
### Table 2: Vasopressor infusion and dose, oxygen administration and method, PO2/FiO2 ratio and vital signs

| Vital signs | Day one | Day two | Day three | Day four | Day five | Day six | Day seven | Day eight | Day nine |
|-------------|---------|---------|-----------|----------|----------|---------|-----------|-----------|---------|
| Temp (°C)   | 38.9    | 40      | 39.8      | 39.8     | 40       | 39.2    | 38.2      | 37.1      | 36.5    |
| PO2/FiO2 ratio | 62.7    | 68      | 114       | 100      | 100      | 136     | 130       | 200       | >400    |
| Oxygen administration and method | NRM 100%/15 lO2 | NRM 100%/15 lO2 | FiO2 1.00 | FiO2 0.65 | FiO2 0.70 | FiO2 0.55 | FiO2 0.45 | Venti mask 60%/10 lO2 | Nasal cannula 6 lO2 | Nasal cannula 6 lO2 |
| Respiratory rate, /min | 49      | 38      | 20        | 20       | 18       | 20      | 16        | 14        | 18      |
| PEEP, mmH2O | -       | -       | 10        | 10       | 10       | 10      | 13        | 7         | -       |
| Total volume, ml | -       | -       | 500-550   | 500-600  | 500-670  | 527-660 | 400-600   | 527-660   | -       |
| Noradrenaline infusion and dose mcg/kg/min | 0.075   | 0.1     | 0.1       | 0.07     | 0.025    | 0.015   | (Only for a few hours) 0.015 | -         | -       |
| Kidney function, ml/kg/hour | 1.84    | 0.98    | 2.72      | 2.57     | 2.21     | 2.08    | 2.53      | 1         | 1.45    |

PO2: Partial pressure of oxygen; FiO2: Fraction of inspired oxygen; PEEP: Positive end-expiratory pressure.

All microbial testing was negative, as was a PCR for COVID-19. No bacteria were isolated in the bronchoalveolar lavage (BAL) specimens. Given that the patient’s symptoms were similar to MIS associated with COVID-19, the patient was started on intravenous immunoglobulin (IVIG) 0.4 g/kg/day, methylprednisolone 62.5 mg three times daily, low molecular heparin 0.6 IU, and aspirin 75 mg daily (Table 3). Despite the negative sepsis screen, we continued the antimicrobial until discharge as initial PCT was elevated.

### Table 3: Pharmacological treatment

| Immunoglobin 0.4 g/kg/day | Day one | Day two | Day three | Day four | Day five | Day six | Day seven | Day eight | Day nine |
|---------------------------|---------|---------|-----------|----------|----------|---------|-----------|-----------|---------|
|                           | 0.4 g/kg/day | 0.4 g/kg/day | 0.4 g/kg/day | 0.4 g/kg/day | 0.4 g/kg/day | 0.4 g/kg/day | 0.4 g/kg/day | 0.4 g/kg/day |          |
| Methylprednisolone         | 62.5 mg x 3 | 62.5 mg x 3 | 62.5 mg x 3 | 62.5 mg x 3 | 62.5 mg x 3 | 62.5 mg x 3 | 62.5 mg x 3 | 62.5 mg x 3 |          |
| Enoxaparin                | 6000 IU x 1 | 6000 IU x 1 | 6000 IU x 1 | 4000 IU x 2 | 4000 IU x 2 | 4000 IU x 2 | 4000 IU x 2 | 4000 IU x 2 |          |
| Aspirin                   | 75 mg x 1    | 75 mg x 1    | 75 mg x 1    | 75 mg x 1    | 75 mg x 1    | 75 mg x 1    | 75 mg x 1    | 75 mg x 1    |          |

### Outcome

The patient’s condition improved with the treatment provided. He remained on mechanical ventilation for six days, and oxygenation returned to near normal by the seventh day. The exanthem disappeared on the fifth day, and the fever settled on the sixth day (Figures 3, 4). Repeat transthoracic echocardiogram (ECHO) on the ninth day showed an improvement to 65%. Noradrenaline was discontinued on the eighth day. The patient was discharged from the ICU fully recovered on day nine.
MIS has been linked with COVID-19. It is likely underdiagnosed, and the pathogenesis remains undefined [2], but there is evidence that its increasing post-COVID-19 occurrence probably shows an association with the dysregulation of the immune system or an antibody-mediated process due to the infection [9,10]. MIS can also occur after an asymptomatic COVID-19 infection in children and adults [11,12]. Although this can result in severe illness, most adult patients survive [10,11].

Bastug et al. illustrated that hypotension, tachycardia, fever, conjunctivitis, diffuse exanthem, dyspnea, and cough are among the most prevalent MIS clinical presentation as well as gastrointestinal symptoms and reduced left ventricular EF. More than 40% of the patients may require vasopressors for hypotension, and almost 20% may require mechanical ventilation [12]. A recent study [10] found that 98% (207 out of 211) of the cases reporting MIS-A had a current or past history of COVID-19 infection, 51% (110 of 214) presented with increased severity of illness requiring vasoactive medications, and 57% were admitted to ICU. Among all patients, 7% died.

The recently published CDC case definition criteria for MIS-A [5] is a step forward for a better understanding of the syndrome and has the potential of encouraging clinicians toward MIS-A reporting, in order to increase...
awareness regarding the syndrome and encourage information sharing. At the time of our patient ICU admission, the case definition for MIS-A was not yet available. Therefore, the identification relied on similar reports found in the published literature [3,4,12,13].

According to recently published criteria on the syndrome [5], the patient’s symptom manifestations, and medical history, we believe our 51-year-old patient met all of the criteria of diagnosis. He presented with fever (>38.0°C) for >24 hours before hospitalization, reduced EF, rash and non-purulent conjunctivitis, and shock, which are not attributable to other causes or medical therapy, elevated CRP and PCT levels, a recent history of COVID-19 infection documented by RT-PCR, and no alternative diagnosis for the illness.

He was characterized as a severe case of MIS-A since respiratory and circulatory support was needed. Management of the patient was guided by the available reports on MIS-A, similar to what has been reported for MIS-C [3,4,12,13]. His clinical condition improved remarkably after the treatment. Although MIS-A associated with COVID-19 is increasingly being reported [4,12], there are no optimal treatment guidelines, and patients in most of the cases are treated similar to the treatment options used in children [14]. However, effective surveillance can provide a better understanding of MIS-A manifestations and potentially can identify more effective therapies or strengthen the current treatment protocols.

Conclusions

Healthy young adult patients may present with severe multiorgan dysfunction several weeks after a mild infection with SARS-CoV-2 requiring respiratory and cardiac ICU support. Since early MIS-A identification plays a significant role in prompt pharmacological treatment initiation and patient recovery, rapid exclusion of other causes is of great importance.

MIS-A identification relies mainly on clinical symptoms; therefore, clinicians should consider MIS-A as a possible cause for patients with SARS-CoV-2 infection history. Local authorities should promote awareness and reporting. Treatment guideline for MIS-A is currently not available, but given the rapid response in our patient, we believe that the MIS-C treatment guideline can be adapted for MIS-A.

Additional Information

Disclosures

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References

1. Multisystem inflammatory syndrome in children and adolescents with COVID-19. (2020). Accessed: May 29, 2021: https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19.
2. Davogusto GE, Clark DE, Hardison E, Yanis AH, Lowery BD, Halasa NB, Wells QS: Characteristics associated with multisystem inflammatory syndrome among adults with SARS-CoV-2 infection. JAMA Netw Open. 2021, 4:e2110323. 10.1001/jamanetworkopen.2021.10323
3. Kofman AD, Sizemore EK, Detelich JP, Albrecht B, Piantadosi AL: A young adult with COVID-19 and multisystem inflammatory syndrome in children (MIS-C)–like illness: a case report. BMC Infect Dis. 2020, 20:716. 10.1186/s12879-020-05439-z
4. Shaigany S, Gnerle M, Guttmann A, et al.: An adult with Kawasaki-like multisystem inflammatory syndrome associated with COVID-19. Lancet. 2020, 396:e8-e10. 10.1016/S0140-6736(20)31526-9
5. Multisystem inflammatory syndrome in adults (MIS-A) case definition information for healthcare providers. (2021). Accessed: November 19, 2021: https://www.cdc.gov/mis/abpp.html.
6. Cyprus. (2021). Accessed: November 19, 2021: https://www.worldometers.info/coronavirus/country/cyprus.
7. Soma VL, Shust GF, Ratner AI: Multisystem inflammatory syndrome in children. Curr Opin Pediatr. 2021, 33:152-8. 10.1097/MOP.0000000000000974
8. Diagnostic testing and screening for SARS-CoV-2. (2020). Accessed: May 3, 2020: https://www.ecdc.europa.eu/en/novel-coronavirus/labouratory-support.
9. Chow EJ: The multisystem inflammatory syndrome in adults with SARS-CoV-2 infection–another piece of an expanding puzzle. JAMA Netw Open. 2021, 4:e2110344. 10.1001/jamanetworkopen.2021.10344
10. Patel P, DeCuir J, Abrams J, Campbell AP, Godfred-Cato S, Belay ED: Clinical characteristics of multisystem inflammatory syndrome in adults: a systematic review. JAMA Netw Open. 2021, 4:e2126456. 10.1001/jamanetworkopen.2021.26456
11. Morris SL, Schwartz NG, Patel P, et al.: 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. 10.15585/mmwr.mm6916e1
12. Bastug A, Aslaner H, Bilir YA, Kemirttek N, Gurosy FM, Bastug S, Bodur H: Multiple system inflammatory...
syndrome associated with SARS-CoV-2 infection in an adult and an adolescent. Rheumatol Int. 2021, 41:993-1008. 10.1007/s00296-021-04843-1

15. Ahsan T, Rani B: A case of multisystem inflammatory syndrome post-COVID-19 infection in an adult. Cureus. 2020, 12:e11961. 10.7759/cureus.11961

14. What’s new in the guidelines. (2021). Accessed: October 19, 2021; https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/.