SARS-CoV-2-induced Multisystem Inflammatory Syndrome in a Young Adult

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Case Report

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Abstract

We describe a case of a previous healthy 20-year-old male athlete who presented with an atypical clinical profile with multiorgan involvement five weeks after confirmed SARS-CoV-2 infection, suggestive for multisystem inflammatory syndrome (MIS). MIS is a rare, potentially life-threatening complication associated with SARS-CoV-2 and shares several similar clinical features with overlapping hyperinflammatory syndromes that may create a great challenge to distinguish between them. MIS should promptly be considered and treated, as uncontrolled MIS has a high mortality.

In MIS cardiac involvement, heart failure may present as an additional problem, especially because volume loading is advised in accordance with proposed therapy. Carefully monitoring of the respiratory and cardiac status in response of resuscitation is therefore warranted.

Introduction

SARS-CoV-2 has globally resulted in more than twenty million of infected cases and deaths [2]. Recent data suggest that in children infected with SARS-CoV-2, the course of the disease is often mild or even sub-clinical [3]. Young adult patients with a new clinical profile manifesting as a hyperinflammatory syndrome, i.e. severe multiorgan involvement, rapidly evolving into acute multiorgan failure, several weeks after infected with SARS-CoV-2, are globally reported [4, 5, 6–15]. They present with a similar pattern of health complaints and clinical course, consisting of persistent high grade of fever (99%), gastrointestinal (94%) and neurological (68%) symptoms, elevated cardiac (75%) and inflammatory biomarkers (99%), and cytopenia (76%). A substantial number of them eventually develop refractory shock requiring vasopressive therapy and invasive mechanical ventilation. This clinical was reminiscent to toxic shock syndrome, Kawasaki disease (KD) and hemophagocytic lymphohistiocytosis (HLH) [1, table 3 in reference 17]. The Centre for Disease Control and Prevention has named this multisystem inflammatory syndrome (MIS).

MIS is a rare but increasingly recognized complication of SARS-CoV-2 infection, usually presenting two up to six weeks after the onset of the COVID-19 infection symptoms [5], and affecting mainly children. Any patient with suspected MIS should be evaluated for infectious and non-infectious etiologies. Early recognition of MIS is important because it is associated with high mortality if left untreated. However, when MIS is suspected, HLH and other overlapping hyperinflammatory syndromes should be in the differential diagnosis. In the present report, we discuss the red flags, diagnostic and therapeutic challenges in MIS triggered by SARS-CoV-2.

Case Description

A previously healthy 20-year-old Caucasian male patient with no medical history, was admitted to our hospital with high fever up to forty degrees Celsius since five days, abdominal pain and diarrhea. There was no history of weight loss or night sweats. Family history of malignancies and inflammatory bowel

diseases were negative. Several weeks before presentation he was infected with SARS-CoV-2 and completely recovered from the infection within two weeks.

We observed an acute ill-painfull-looking young man. Physical examination revealed a blood pressure of 95/40 mmHg with sinustachycardia of 110 beats per minute, a respiratory rate of twenty-four per minute, pulse oximetry of 97% without supplied oxygen, and temperature of 39.8 degrees Celsius. Remaining clinical examination displayed no meningism signs, no cardiac murmurs, no skin abnormalities, and a soft abdomen with pressure pain in the lower right part at the McBurney's point. Laboratory testing revealed high levels of inflammatory biomarkers, including ferritin, elevated lactate dehydrogenase and liver enzymes, and normocytic anemia without signs of hemolysis [see Table 1, Fig. 1]. The contrast enhanced computed tomographic scan (CT) of the thorax and abdomen revealed splenomegaly and thickening of the terminal ileum in a long traject of at least twenty centimeters. No pulmonary infiltrates or signs of malignancy were detected. The SARS-CoV-2 PCR on a smear from the throat and nose and the SARS-CoV-2 IgG antibody titre (94.7 AU/mL) were positive. Serology was negative for Human immunodeficiency virus, Cytomegalovirus and Epstein-Barr virus. Blood, urinary and feces cultures were negative. An infectious terminal ileitis was suspected for which patient received broad-spectrum antibiotic therapy (cefuroxime and metronidazole). Despite this therapy the patient's clinical course showed no improvement in a couple of hours. A worsening with additional neurological symptoms followed. The patient did not fulfill the criteria for HLH, macrophage activation syndrome or KD. MIS was suspected and prednisolone 60mg once daily was started shortly after admission [see Table 1 in reference 17].

Table 1

Patient characteristics during and after hospitalization

	Day 0	Day 2	Day 6	1 week after discharge	4 weeks after discharge	Reference values*
Hemoglobin (g/dL)	7.7	7.2	8.0	8.6	9.1	12 – 18 g/dL
White-cell count (10^9 cells/L)	6.9	6.5	13.6	15.9	5.8	4 – 11x10^9 cells/L
Platelet count (10^9 cells/L)	133	113	368	596	248	150 – 400x10^9 cells/L
Lactate dehydrogenase (U/L)	418	379	335		197	<250 U/L
Ferritin (µg/L)	3300	7400	4100	1300	190	20 – 300 µg/L
CRP (mg/L)	310	144	29	3	< 3	0 – 8 mg/L
Procalcitonin (ng/L)	8.1	8.0	0.82			0 – 0.5 ng/L
D-dimer (mg/L)	7.44	4.37				2.0 – 4.0 mg/L
Fibrinogen (mg/L)	1050	1480				1600 – 3200 mg/L
Hs Troponin I (ng/L)	3	158	48		6	0 – 47 (ng/L)
nT-proBNP (ng/L)	120	2538	756		< 35	0 – 125 (ng/L)

Thirty hours later the patient's condition deteriorated rapidly with additional chest pain and hemodynamic instability, i.e. resuscitation refractory hypotension (80/39 mmHg) with sinustachycardia of 115 beats per minute. Laboratory tests showed increased ferritin levels, pancytopenia and elevated inflammatory and cardiac biomarkers. Electrocardiogram revealed no abnormalities. Broadening of the antibiotic regimen with gentamicin, intravenous immune globulins (IvIG) during two days (2g/kg, 150 grams and 1g/kg, 80 grams respectively), and aspirin (200mg daily) were initiated. After fluid resuscitation accompanying immune globulin treatment, respiratory failure occurred. The CT-angiography of the chest did not show evidence of pulmonary embolism or infiltrates. The echocardiogram revealed a moderately reduced systolic left ventricular function with estimated ejection fraction of below 40%, with global hypokinesia without regional wall motion abnormalities related to a circulation area of a specific coronary artery [see Fig. 2]. Cardiac involvement as part of MIS was hypothesized. High-flow oxygen therapy was started, after which his respiratory condition recovered well within 24 hours. Follow-up echocardiography showed improvement of left ventricular systolic function with estimated ejection fraction of 50%.

Forty-eight hours after completing the therapy with IvIG and the started higher doses of prednisolone and aspirin, the patient's clinical condition and laboratory tests normalized gradually [see Table 1, Fig. 1]. The therapy with prednisone was continued in the following schedule: 80mg twice daily during a day, followed by 80mg once daily during five days, followed by 40mg once daily from the date of discharge. The patient could be discharged on the eleventh day of hospitalization. The discharge medication consisted of prednisolone 40mg once daily in phase-out schedule tapered over at least a week, a total of twenty-two days of treatment, aspirin 200mg once daily with omeprazole to be continued for a total of forty days. The first outpatient follow-up visit, seven days after discharge, showed further signs of health recovery, i.e. no recidive of fever and declining inflammatory parameters. An echocardiogram will follow 6 weeks after discharge.

Discussion

The described MIS in this patient was characterized by by a wide range of atypical symptoms. The patient presented to our hospital within a time period of five weeks after being tested positive with the SARS-CoV-2. This similar interval between confirmed infection with SARS-CoV-2 and the onset of symptoms belonging to MIS is described in recent cases and made us hypothesize the patient would have MIS.

MIS shares many of the key clinical features with several overlapping hyperinflammatory syndromes, each with its own distinctive treatment, suggesting that MIS is part of a broad spectrum of diseases [1, table 3 in reference 17]. A recent positive SARS-CoV-2 serology test is the differentiating key factor of MIS from the overlapping syndromes. Because untreated MIS and other overlapping hyperinflammatory syndromes both are associated with a high mortality, it is important to also consider one of the overlapping hyperinflammatory syndromes in patients presenting with a condition of MIS or vice versa.

So far, mainly children with a subclinical infection with SARS-COV-2 that develop MIS have been described. Our patient was adult and initially did not have pulmonary symptoms, arterial hypoxemia, or radiographic distinctive features. Early echocardiogram revealed a depressed systolic left ventricular function without pericardial effusion [see Fig. 2]. Pulmonary embolism and infectious pulmonary infiltrates were ruled out. The left ventricular function largely improved after high-flow oxygen and diuretic therapy. The observed positive effects of diuretics on the clinical course and systolic ventricular function, suggest that iatrogenic fluid overload after resuscitation during 72 hours may be the main underlying cause of the observed heart failure. However, the cardiac biomarkers and systolic ventricular function have not been completely recovered after the therapy, therefore cardiac involvement as part of MIS is very likely. Resuscitation remains part of the proposed therapy in patients with severe MIS, but heart failure may be a relevant clinical problem. Therefore monitoring of the cardiac status in response of the fluid therapy is warranted.

Cardiac manifestations in the light of MIS are seen in up to 80% of the cases, including arrhythmia, coronary artery involvement and even aneurysms in addition to the above mentioned cardiac aspects [6].

The most severe cases may present cardiogenic shock requiring fluid resuscitation, vasopressive therapy, mechanical ventilation and in exceptional cases even ECMO therapy (extracorporeal membrane oxygenation). Most of the affected patients (up to 78%) show full recovery of their left ventricular function, while up to 22% retail mild to moderate permanently decreased function after adequate therapy [7–10].

The cornerstone of treatment in MIS is immune-modifying therapy to reverse the inflammatory response in cases with signs of cardiac involvement, excessive increase of inflammatory parameters or refractory shock. Although the exact effectiveness on long-term remains unclear, patients in limited case series show promising results [4, 11–16]. The recommended doses of IvIG for patients with KD-like characteristics is the same as is used for KD, 2 grams/kg body weight over a period of 8 to 12 hours [11]. For the recommended dose of glucocorticoids, methylprednisolone during early life-threatening stage, a regimen of 2 mg/kg body weight daily seems reasonable. When the disease has reached complete remission, and the patient has improved clinically to be dismissed from hospital, the oral dose of prednisolone can be reduced over a period of weeks to minimize the risk of relapse. The supporting proof for using immune-modifying therapy is from previous case series, describing similar patient populations in same health conditions, like KD, HLH and toxic shock syndrome. In these case series 75% of the cases were treated alike with IvIG, who showed clinical and cardiac recovery after treatment [4, 12–15]. In other limited case series approximately 55% of the patients were treated with glucocorticoids in different doses. Prior to administrating IvIG in these patients, it is indispensable to obtain blood for blood cultures in analysis of possible pathogens and serologic SARS-CoV-2 test.

In the later stage we added IvIG with high doses of aspirin to the therapy due to refractory shock and concerns of cardiac involvement. Within 48 hours after the onset of this therapy, his clinical condition recovered considerably and cardiac left ventricular function has partially been restored up to 47%.

The risk of a relapse of and long-term complications from MIS after ceasing of the glucocorticoids, whether or not luxated by another pathogen, remain unknown. Complementary data are not available yet. Physicians should be aware of MIS during the first six weeks after an infection with SARS-CoV-2, so targeted therapy may promptly be initiated.

Conclusions

SARS-CoV-2-associated MIS is a rare emerging clinical entity and has clinical features similar to several overlapping hyperinflammatory syndromes. Mainly children are affected several weeks after infection with SARS-CoV-2. Despite the similarities between MIS and other hyperinflammatory syndromes, MIS typically presents several weeks after SARS-CoV2 infection. Timely treatment with glucocorticoids, IvIG and high doses of aspirin for those patients who are suspected for MIS should usually be sufficient to treat the inflammatory state. Further research is needed to clarify the aspects in the pathogenesis of MIS in young adult patients to improve effective targeted intervention.

Declarations

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Conlicts of interest / Competing interests

All authors declare that they have no competing interests.

Ethics approval

Not applicable

Consent to participate

The participant has consented to the submission of the case report to the journal

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request

Availability of data and material

The data that support the findings of this study are available from the patient record system “HIX” at the Jeroen Bosch Hospital in The Netherlands, but restrictions apply to the the availability of these data, which were used under license for the current case report, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of patient.

Code availability

not applicable

Authors' contribution Author's contributions

Haldun Bulut (HB), the first author of this report, was the main involved clinical medical doctor in the whole case. HB collected almost all data, searched for available relevant literature, performed the analysis, designed and directed the study, organized the report-writing team at the different departments and was the major contributor in writing this manuscript.

Hendrik J.M. de Jonge (HJM) was the first medical doctor who was involved in the diagnostic traject of our patient at the emergency department. HJM organized the initial diagnostic traject at the clinical department of gastroenterology and ruled out the possibility of an inflammatory bowel disease. HJM immediately contacted AHE Herbers (AHE) for further advices. HJM also contributed in writing the case presentation part of our report.

AHE collected most of the diagnostic data and was the first medical doctor who diagnosed the syndrome post-SARS-CoV-2. AHE also contributed in conceiving, designing and analyzing the data and results. AHE contacted the colleagues for collaboration at the academic Radboud medical center in Nijmegen.

Robert Joustra (RJ), Paetrick Netten (PN), Ilse Hageman (IH), Peter de Jager (PJ) and Frank L. van de Veerdonk (FV) all contributed to the design and implementation of the report, to the analysis of the results and to the writing of the final version of this manuscript. All authors read, discussed the results and approved the final manuscript.

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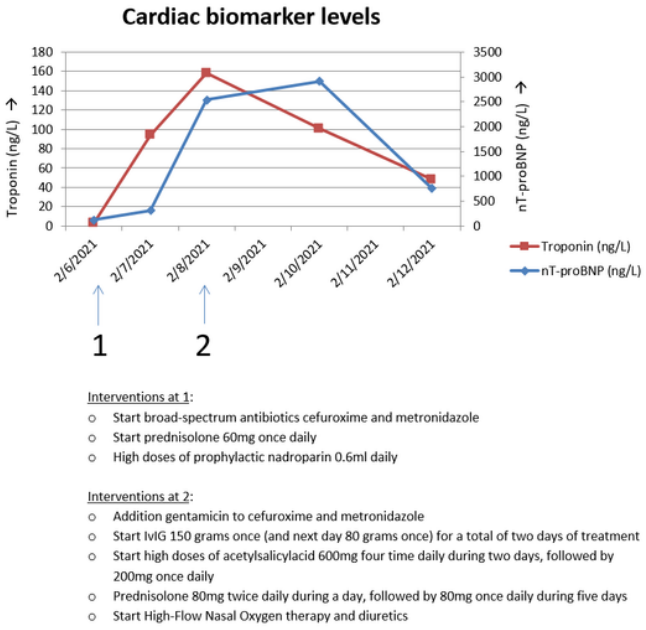
Figures



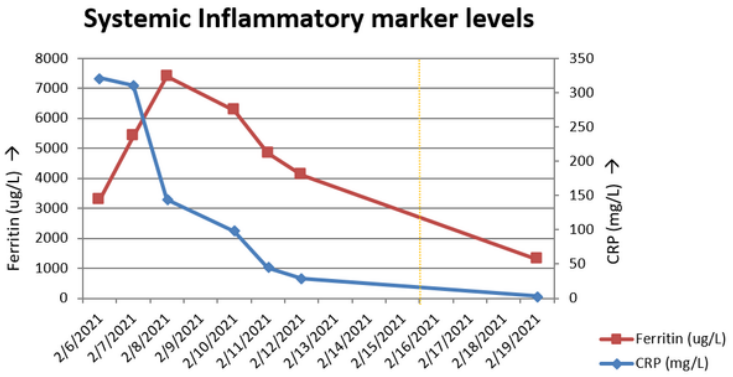
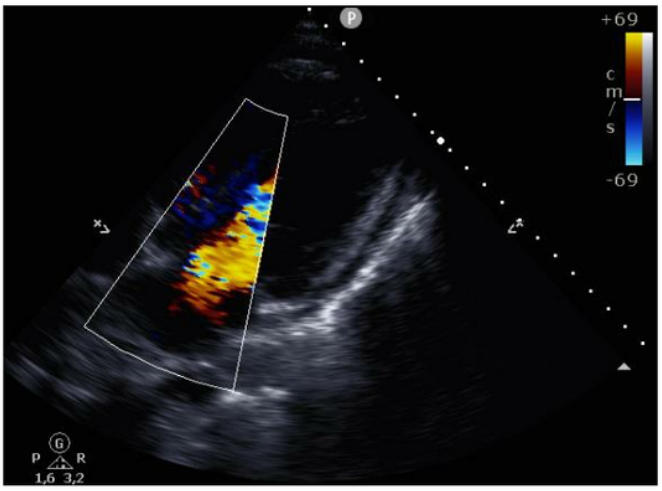
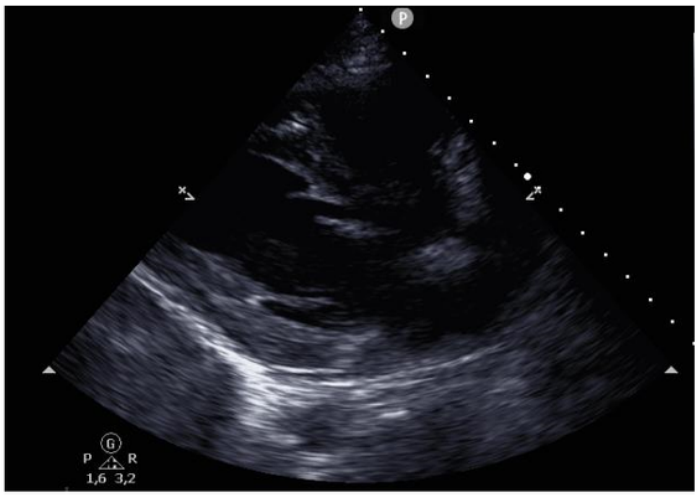


Figure 1

A: Timeline of cardiac biomarker levels in response to interventions throughout hospital stay B: Timeline of the inflammatory marker levels in response to the described interventions above



A



B

Figure 2

Images of echocardiogram at hospitalization day 2; Suspicion on cardiac involvement as part of MIS The panels below demonstrate depressed systolic left ventricular function, slight Tricuspidal valve insufficiency, Aotic valve with 3 leaflets without pericardial effusion and a dilated Vena Cava Inferior.