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CASE SERIES
Heart failure

Multisystem inflammatory syndrome-related refractory cardiogenic shock in adults after coronavirus disease 2019 infection: a case series

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Background A novel multisystem inflammatory syndrome in children (MIS-C) temporally associated with the coronavirus disease 2019 (COVID-19) infection has been reported, arising weeks after the peak incidence of COVID-19 infection in adults. Patients with MIS-C have been reported to have cardiac involvement and clinical features overlapping with other acute inflammatory syndromes such as Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome. Multisystem inflammatory syndrome in children may follow COVID-19 infection, most of the time after its asymptomatic form, even though it can lead to serious and life-threatening illness.

Case summary In this case series, we discuss two cases of young adults with no former medical history who fit with the criteria defined in MIS-C. They both developed a refractory cardiogenic shock and required intensive care treatment including mechanical circulatory support, specifically the use of venous–arterial extracorporeal membrane oxygenation. They were both treated early with intravenous immune globulin and adjunctive high-dose steroids. They recovered ad integrum in less than 2 weeks.

Discussion Multisystem inflammatory syndrome in children occurs 2–4 weeks after infection with severe acute respiratory syndrome coronavirus 2. Patients with MIS-C should ideally be managed in an intensive care environment since rapid clinical deterioration may occur. It would be preferable to have a multidisciplinary care to improve outcomes. Patients should be monitored for shock. Elucidating the mechanism of this new entity may have importance for understanding COVID-19 far beyond the patients who have had MIS-C to date. The pathogenesis seems to involve post-infectious immune dysregulation so early administration intravenous immune globulin associated with corticosteroids appears appropriate. It implies early recognition of the syndrome even in young adults.

Keywords Multisystem inflammatory syndrome in children • Case report • Refractory cardiogenic shock • Venous–arterial extracorporeal membrane oxygenation • Coronavirus disease 2019

ESC Curriculum 2.3 Cardiac magnetic resonance • 6.4 Acute heart failure • 7.3 Critically ill cardiac patient • 7.1 Haemodynamic instability

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Learning points

- Multisystem inflammatory syndrome in children following severe acute respiratory syndrome coronavirus 2 infection may lead to multi-visceral dysfunction, sometimes with refractory heart failure requiring venous–arterial extracorporeal membrane oxygenation.
- This syndrome has been well described in healthy children but in this case, it occurs in young adults.
- Delayed onset after infection which suggests that the pathogenesis involves post-infectious immune dysregulation.
- The majority of affected patients should be treated with intravenous immunoglobulins, and also received adjunctive high-dose steroids.
- Early recognition of the syndrome even in young adults is needed for better prognosis.

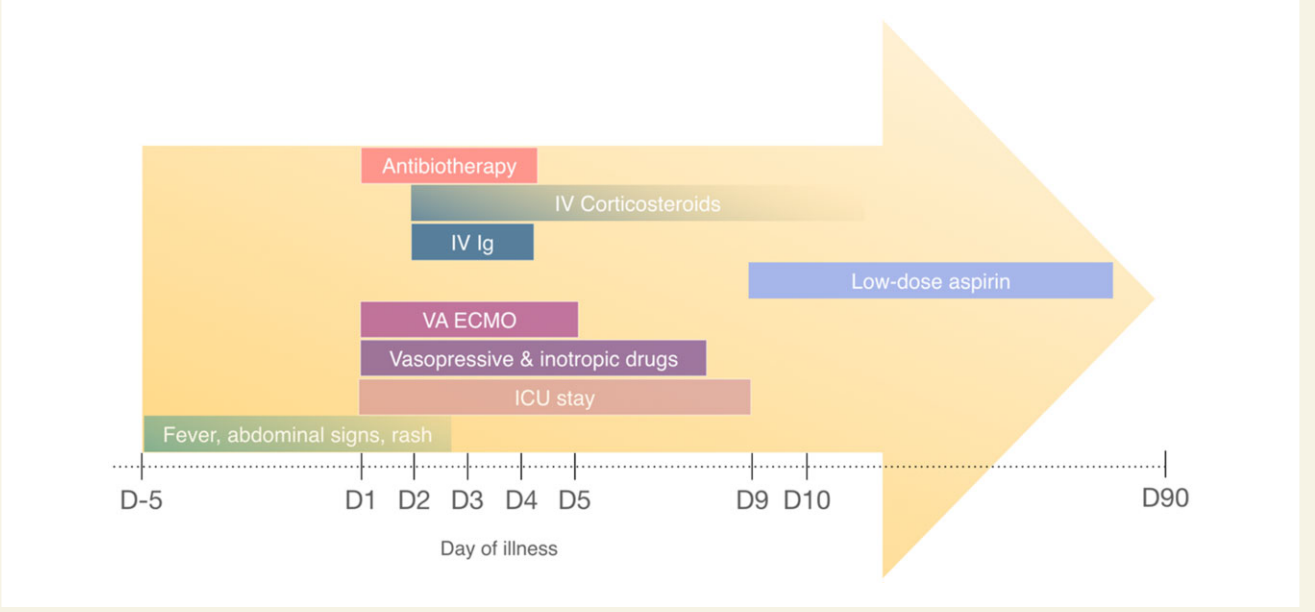
Introduction

First noticed in a cluster of patients in China's Hubei Province in December 2019, coronavirus disease 2019 (COVID-19) was declared a global pandemic on 11 March 2020 by the World Health Organization. It is well known that the main target of COVID-19 is the pulmonary system. Indeed, severe COVID-19 represents viral pneumonia from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leading to acute respiratory distress syndrome (ARDS). Ultimately, in patients with therapy refractory severe ARDS, the application of extracorporeal membrane oxygenation (ECMO) represents a treatment option.[1]

Severe acute respiratory syndrome coronavirus 2-induced infection is associated with pulmonary and extrapulmonary manifestations, foremost amongst which are cardiological lesions with acute myocardial injury, which we report herein.[2] It is not clearly understood how COVID-19 compromises the cardiovascular system; still, we can keep back as possible mechanisms: direct myocardial injury, indirect injury through cytokine release, a microvascular thrombosis caused by the prothrombotic state, and exacerbation of underlying cardiovascular disease (e.g. plaque rupture in susceptible patients).[2–4] In rare instances, it can even lead to cardiovascular collapse. Hekimian *et al.*[5] described four different aetiologies of COVID-19-related cardiogenic shock, which may require venous–arterial ECMO (VA-ECMO) support: fulminant myocarditis, myocardial infarct, pulmonary embolism, and multisystem inflammatory syndrome in children (MIS-C). In spring 2020, MIS-C or paediatric multisystem inflammatory syndrome begins to be described, first in the UK[6] and Italy,[7] then in the USA and other parts of Europe. Analogies were rapidly made with Kawasaki disease (KD), toxic shock syndrome, and secondary haemophagocytic lymphohistiocytosis/macrophage activation syndrome.[8]

However, recent clinical, microbiological, and immunological reports describe MIS-C as a new immunopathogenic disease.[9–11] According to the different definitions of MIS-C,[12] it appears to be a rare complication occurring only in child population. Even more, this syndrome begins to be described in adults.[13] Herein we will discuss the special case of two adults with MIS-C, who all needed organ support by VA-ECMO.

Timeline



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Case presentation

While France was in the middle of the second wave of COVID-19, two male patients, aged 27 (Patient 1) and 18 (Patient 2) years old, with no former medical history were admitted to the intensive care unit (ICU) with similar symptoms.

They had no previous history of COVID-19 symptoms or contact with known COVID-19 cases.

They both describe flu-like syndrome about 3 weeks before their hospitalization.

At their admission, (Day 1) they declared exactly similar symptoms including fever during at least 72 h, cutaneous and mucosal rash (*Figure 1A* and *C*), gastrointestinal symptoms with pain, diarrhoea, nausea, and vomiting, uveitis for only one of them (*Figure 1B*). Then, both patients were rapidly (Day 1) admitted to ICU because of haemodynamic failure. All clinical and biological characteristics of the two patients at ICU admission are summarized in *Table 1* and *Figure 2*. Indeed, they developed severe cardiogenic shock (lactate ≥ 4 mmol/L) with predominant left ventricular failure (LVEF $\leq 35\%$), increased high-sensitive cardiac troponin T 10 times upper limit of normal (hs-cTnT > 10 ULN/99th percentile of 14 ng/L) and requirement for inotropic and vasopressor drugs. Severe acute respiratory syndrome coronavirus 2 serology [checked before treatment with intravenous immunoglobulin (IVIg)] was strongly positive, suggesting recent exposure to SARS-CoV-2.

On admission, the patients also have severe acute kidney injury KDIGO 2 and hepatic failure associated with a strong biological inflammatory syndrome (*Table 1*).

In the view of multi-visceral involvement and refractory haemodynamic instability, both were equipped with VA-ECMO on Day 1. They both had a SAVE-Score of 3 and high-dose vasoactive support with vasoactive-inotropic score (VIS) of 22 for Patient 1 and 81 for Patient 2. It was decided to install the ECMO under regional anaesthesia because the method had the advantage of avoiding haemodynamic stress from general anaesthesia medication. A broad-spectrum, empirical antibiotherapy combining a 3rd-generation cephalosporin (Cefotaxime) and a macrolide (Azithromycin) was introduced on Day 1 for both patients and then stopped on Day 4 because bacteriological examinations were negative. Multiple tests and examinations were initiated to identify the trigger of the cardiogenic shock. These examinations included bacterial assays (blood, urine, and stool culture, and throat PCR), viral assays (HIV, EBV, CMV, HSV, and hepatitis), zoonoses research, large autoimmune screening, and abdominal scan. All of them remained negative. A SARS-Cov-2 serology (EUROIMMUN Elisa Technic, IgG/IgA) was highly positive for both patients, leading us to make the diagnosis of MIS-C. A computed tomography coronary angiograms completed by a coronary angiography were also realized to totally exclude obstructive epicardial coronary artery disease and practice a biopsy. Cardiovascular magnetic resonance, realized on Day 7 for both patients, shown a diffuse myocardial oedema with T2 measured at 60 ms at 1.5T (*Figure 3A*) and a late gadolinium enhancement pattern with pericardial effusion, all related with myo-pericarditis (*Figure 3B*). A histological analysis of an endomyocardial biopsy realized during coronary angiography for Patient 2 was also suggestive of the diagnosis, showing a diffuse non-specific myocarditis with dense inflammatory cell infiltrate (white arrows)

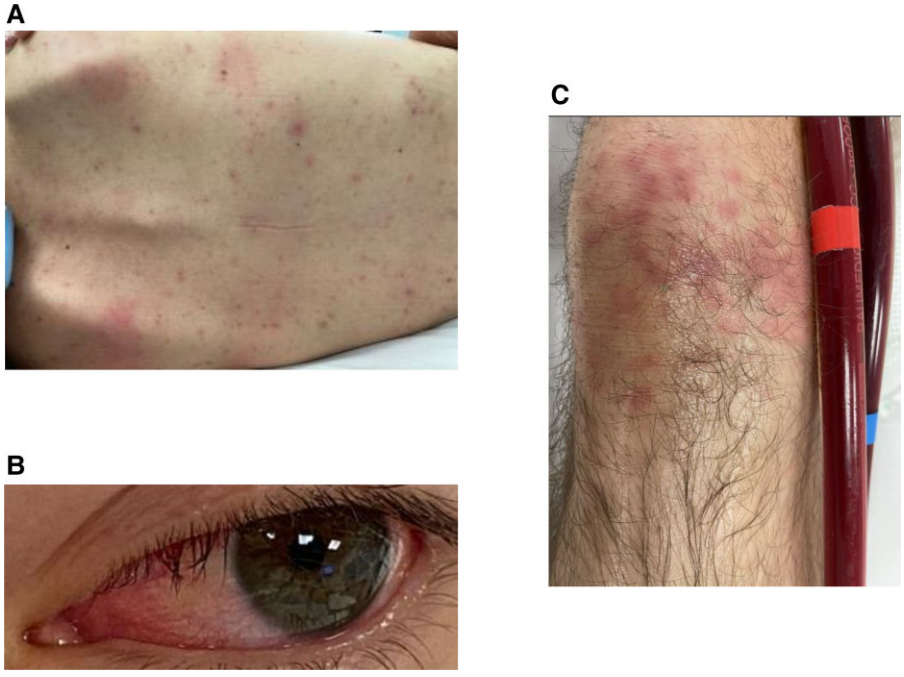


Figure 1 Rash (*A*) in Patient 1, uveitis (*B*), and rash (*C*) in Patient 2.

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Table 1 Clinical characteristics for the two patients

	Patient 1	Patient 2
Age (year)	27	18
Gender	Male	Male
IMC	21	23
ABO blood group	O+	A+
Charlson score	0	0
IGS 2 score at ICU admission	49	53
SOFA score at ICU admission	8	11
Respiratory SOFA	0	1
Haemodynamic SOFA	3	4
Renal SOFA	2	2
Liver SOFA	2	2
Coagulation SOFA	1	2
Neurological SOFA	0	0
Multisystem organ involvement	3	4
SAVE-score at ICU admission	3	3
Cardshock score at ICU admission	4	3
VIS Score at ICU admission	22	81
Lactate level at ICU admission (mmol/L)	6,5	4
Serum IL-6 level at ICU admission (pg/mL)	317	420
Ferritin level at ICU admission (mcg/L)	>8000	2234
hs-cTnT level at ICU admission (ng/L)	818	1858
D-Dimer level at ICU admission (mcg/mL)	>20	17
Visual LVEF at ICU admission	20%	35%
Days from symptoms onset to hospitalization	5	4
Days from hospitalization to ICU admission	0	0
Days from ICU admission to VA-ECMO	0	0
Duration of catecholamine use (days)	7	8
Duration of organ failure (days)	4	5
VA-ECMO duration (days)	4	5
Length of stay in ICU (days)	8	9
Length of stay in hospital (days)	24	18
Mortality at Day 90	0	0

between the cardiomyocytes (*Figure 4C*), composed mainly with macrophages (*Figure 4B*), lymphocytes (*Figure 4A*), and neutrophils. Cardiomyocyte damages in the form of nuclear loss (black arrows), eosinophilic cytoplasmic homogenization, or necrosis are present (*Figure 4C*). On Day 2, for both patients, we introduced a treatment with IVIg 1 g/kg/J for 2 days associated with methylprednisolone 2 mg/kg per day for 5 days, then progressively decreased. We report a good tolerance with no side effects during treatment. Also, an effective treatment with unfractionated heparin (target therapeutic range of activated partial thromboplastin time 60 s) was conducted on Day 1. The inflammatory syndrome resolved quickly after the initiation of the combination therapy (*Figure 5*). When the weaning trial was haemodynamically well tolerated without the need for increasing inotropic or vasoactive support and echo-cardiographic criteria were fulfilled (LVEF > 20–25%, time-velocity integral >10 cm, lateral mitral annulus peak systolic velocity >6 cm/s, satisfactory right ventricular systolic function without dilatation), the weaning procedure was performed on Day 4 for Patient 1 and on Day 5 for Patient 2. Outcomes were similar for both patients, with full and complete recovery of cardiac function, allowing norepinephrine weaning, respectively, on Days 7 and 8. Both patients were discharged from ICU on Day 8 for Patient 1 and on Day 9 for Patient 2, on low-dose acetylsalicylic acid. The 1- and 3-month follow-up echocardiography related full recovery (LVEF > 65%). Three months later, both patients are still alive at home.

Discussion

Symptoms, chronology of onset, imaging, absence of other alternative diagnoses, for each of the two patients, fit with the criteria defined in MIS-C,[12] except for the age.

Corticosteroid treatment is a commonly used adjunctive therapy to IVIg for treatment in the paediatric population.[8] This treatment

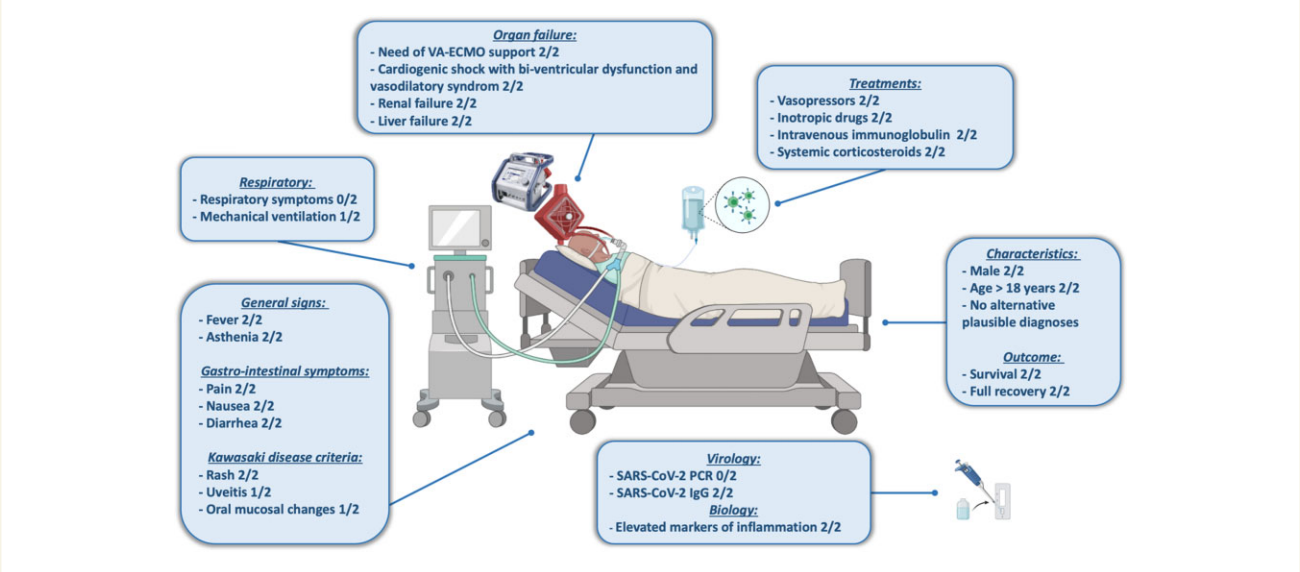
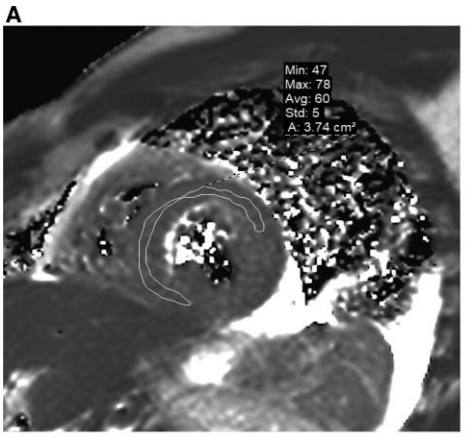


Figure 2 Clinical features, disease time-course, and responses to treatment for the two MIS-C patients.

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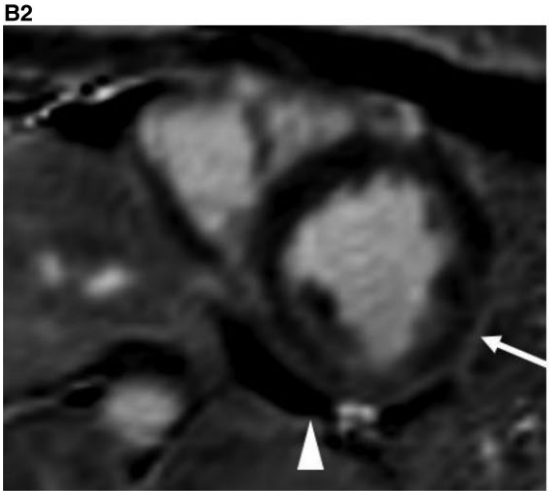


Figure 3 Cardiac magnetic resonance imaging. (*A*) Patient 1 cardiac magnetic resonance, T2 mapping sequence in a short-axis plane at the mid-ventricular level showing diffuse myocardial oedema with T2 measured at 60 ms at 1.5 T. (*B1*) Patient 2, sequence of late enhancement in four cavities showing a no signal intensity pericardial effusion (white arrowhead) and contrast enhancement of the lateral wall (white arrow) (*B2*) (rt short axis): Patient 2, Sequence of late enhancement in a minor axis plane in the medium region showing contrast enhancement of the lateral wall (white arrow) and pericardial effusion (white arrow head) (*C*) Heart parameters for each patient.

was prescribed because all clinical features were comparable and there was no alternative plausible diagnosis. To our knowledge, no other treatment has been tried in this pathology. Total recovery was observed.

The recent emergence of MIS-C explains the lack of randomized trials, and therapeutic management is largely based on knowledge of KD and the suspected pathophysiology of MIS-C.

Elucidating the mechanism of this new entity may have importance for understanding COVID-19 far beyond the patients who have had MIS-C to date, who are relatively few in numbers as compared with those who have had SARS-CoV-2 infection. Because MIS-C generally occurs late after SARS-CoV-2 infection, after antibody has developed, aberrant cellular or humoral adaptive immune responses may be involved.[8,12] This contrasts with the mechanism of myocarditis related to COVID-19 in which the virus represents the direct pathogen of the myocardial cells. The understanding of MIS-C might illuminate the elusive pathogenesis of KD. Multisystem inflammatory syndrome in children may look more like microangiopathy while KD affects larger vessels more. The good response to treatment with immunoglobulins and corticosteroids would argue for this hypothesis of pathology mediated by autoantibodies. The relationship of MIS-C to SARS-CoV-2 infection suggests that the pathogenesis involves post-infectious immune dysregulation.[8,10]

Additional studies could be initiated to confirm the place of this treatment in adults.

To our knowledge, this is the third report case of adult MIS-C related to SARS-CoV-2 infection,[14,15] but the first one relating VA-ECMO Life Support for refractory cardiogenic shock with favourable outcomes.

Conclusion

As it seems to appear in this case report, the MIS-C, which is now well known in the child population, can also appear in adults. In rare cases, it can even lead to cardiac failure resulting in organ support by VA-ECMO. In the light of this fact, this syndrome should be in situations of idiopathic cardiogenic shocks. Its early recognition could allow early initiation of this effective therapeutic

C

	Patient 1	Patient 2
LVEF	54%	58%
Left ventricular Telediastolic Volume	59 mL/m2	80 mL/m2
Left Ventricular Telesystolic Volume	28 mL/m2	33 mL/m2
Myocardic mass	73 g/m2	75 g/m2
RVEF	55%	53%
Right Ventricular Telediastolic Volume	65 mL/m2	70 mL/m2
Right Ventricular Telesystolic Volume	30 mL/m2	33 mL/m2
Left Auricular Volume	31 mL/m2	30 mL/m2
Late gadolinium enhancement	Negative	Positive 4/17 segments 24% of myocardic mass

Figure 3 Continued

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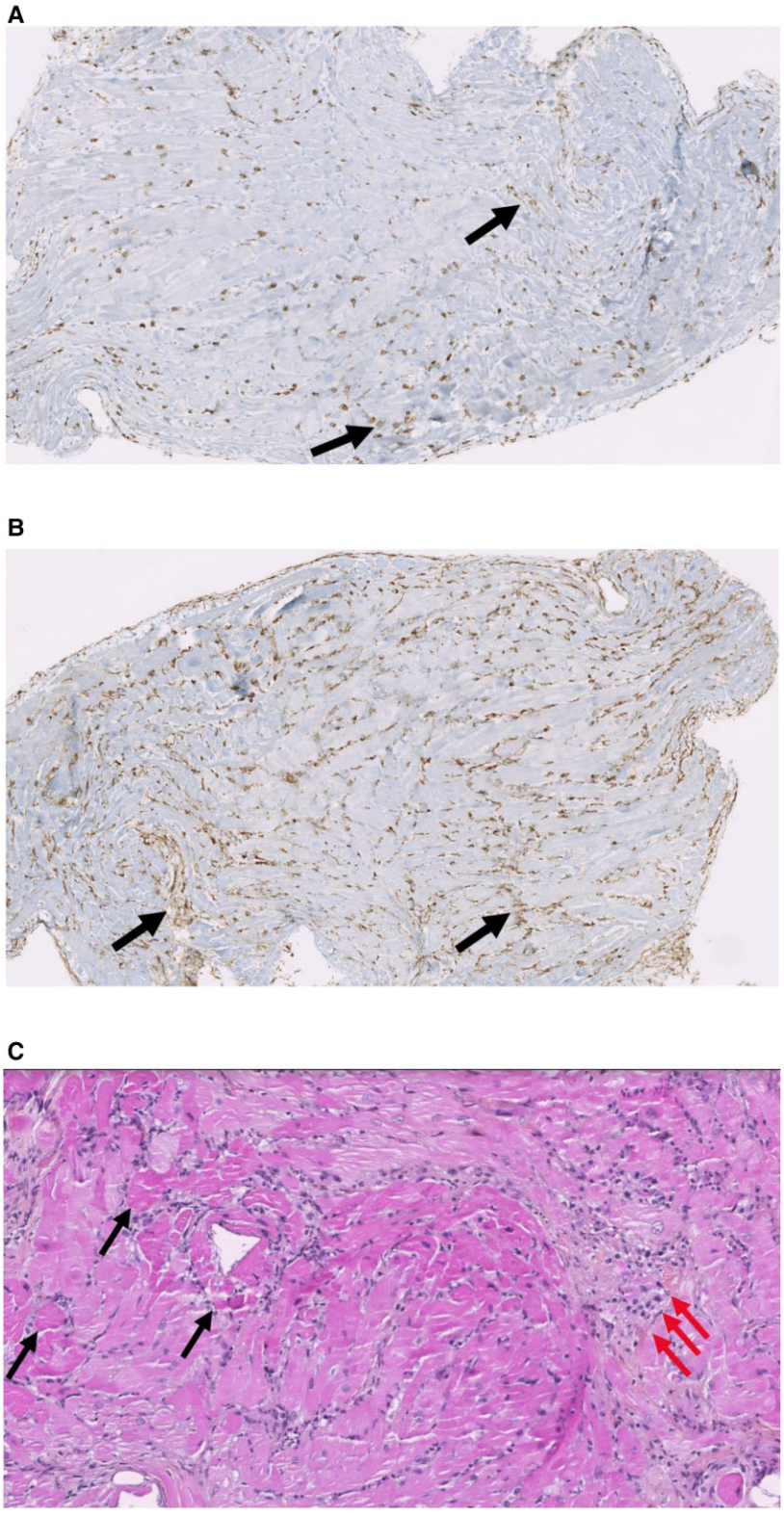


Figure 4 Histological analysis of an endomyocardial biopsy realized during coronary angiography for Patient 2. Immunohistochemical staining (arrows) of T lymphocytes and macrophages with an anti-CD3 antibody (*A*) and an anti-CD68 antibody (*B*), respectively (original magnification ×100). (*C*) Endomyocardial biopsy showing a diffuse non-specific myocarditis with dense inflammatory cell infiltrate (3 tight arrows) between the cardiomyocytes, composed mainly with macrophages, lymphocytes, and neutrophils. Cardiomyocyte damages in the form of nuclear loss (3 distant arrows), eosinophilic cytoplasmic homogenization, or necrosis are present (haematoxylin–eosin–saffron, original magnification ×200).

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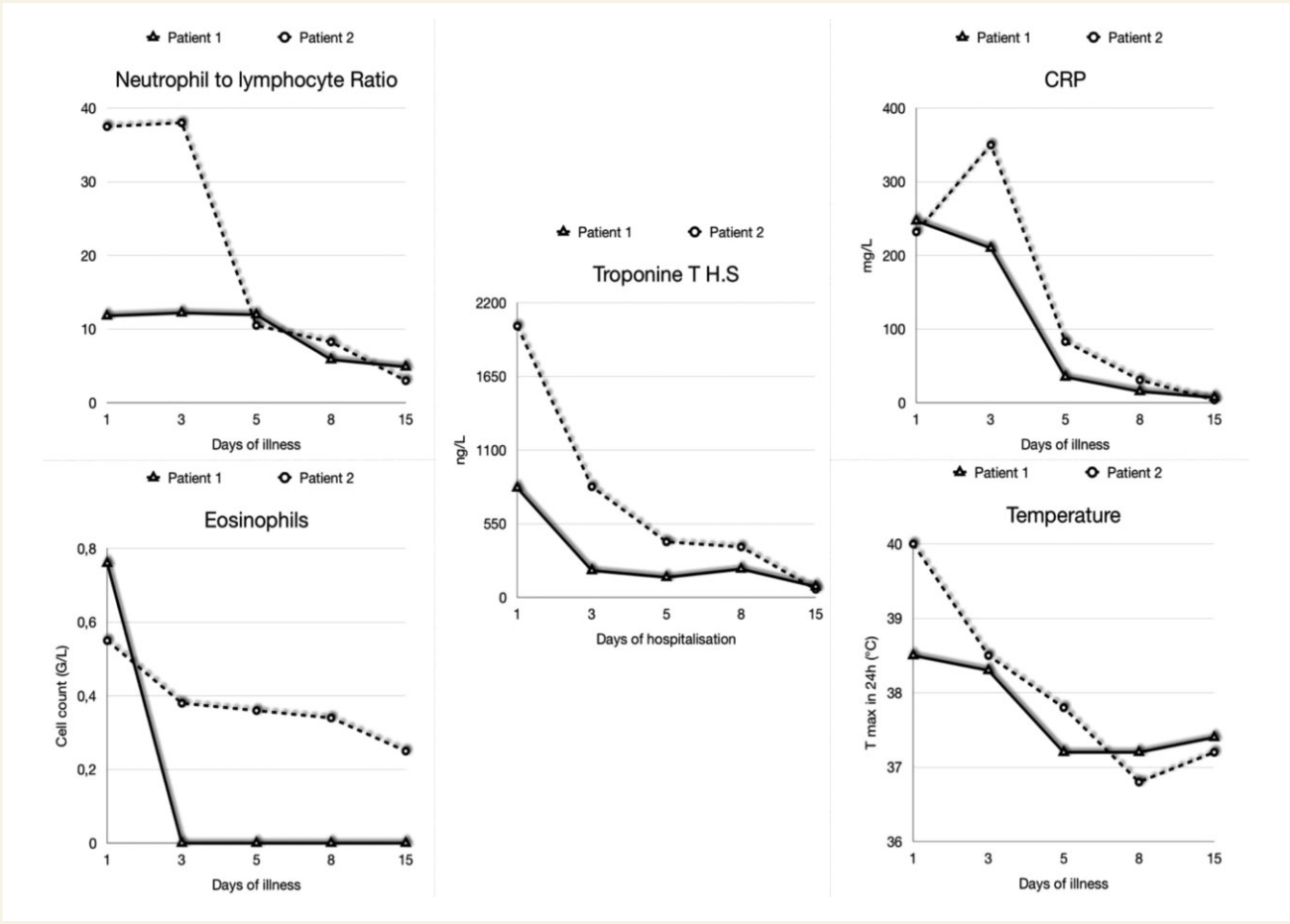
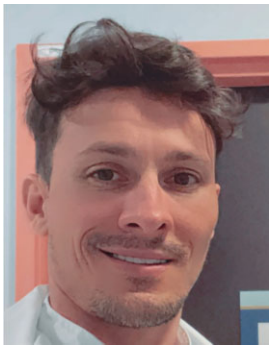


Figure 5 Evolution of main biological markers of severity along hospitalization.

combination of IVIg and steroids which in turn conditions a complete recovery.

Lead author biography



David is a senior anaesthesiologist and intensivist in the department of cardiovascular surgery, La. Timone University Hospital, Marseille, France. He is at the origin of a database of COVID-19 patients admitted to the 6 intensive care units of Marseille University Hospital.

Ethical approval

This study was approved by the local Ethics Commission (2020-53) and the French Society of Anaesthesia and Critical Care (00010254-2020-06).

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports* online.

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Consent: The author/s confirm that written consent for submission and publication of this case series including image(s) and associated text has been obtained from the patient in line with COPE guidelines.

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