Journal of Paediatrics and Child Health

doi:10.1111/jpc.15520

INSTRUCTIVE CASE

Cardiac injury and vasoplegia in critically ill children due to multisystem inflammatory syndrome in children associated with COVID-19

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Since April 2020, paediatric intensive care societies resonated alerts regarding the emergence of a multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. The World Health Organization produced a preliminary case definition to help standardise and define MIS-C.[1] Clinical criteria included fever for more than 3 days and two of the following: rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs, hypotension or shock, features of cardiac involvement, coagulopathy and acute gastrointestinal problems. Laboratory criteria included elevated inflammatory markers and the exclusion of other identifiable microbial causes. Inclusion criteria were the evidence of COVID-19 or contact with patients with COVID-19. Progression to warm, vasoplegic shock, refractory to volume resuscitation, and demanding haemodynamic support were seen in several cases. In addition to the supportive care, there were recommendations for anti-inflammatory strategies including intravenous immunoglobulin (IVIG), steroids and immunomodulators.

We report the first Portuguese case of an adolescent with MIS-C presenting with vasoplegic shock and cardiac injury, with the need for respiratory and cardiovascular support.

Key Points

1 Multisystem inflammatory syndrome in children presents with hyper-inflammation that can affect the heart, progress to warm, vasoplegic shock, refractory to volume resuscitation, and eventually require haemodynamic support.
2 Elevation of troponin and brain natriuretic peptide (pro-BNP) during hospitalisation are important markers of prognosis and should be seen as warning signs.
3 Treatment using anti-inflammatory strategies such as intravenous immunoglobulin and steroids showed benefits.

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Conflict of interest: None declared.

Accepted for publication 13 April 2021.

Case Report

A healthy 13-year-old boy was hospitalised with a 3-day high fever and an erythematous macular rash in the hypothenar region. Blood examination revealed lymphopenia (700 lymph/mm^3) and increased C-reactive protein (175 mg/L) and D-dimers (631 µg/L). Chest radiography showed a bilateral interstitial infiltrate. The polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) of the nasopharyngeal swab was negative, but his mother had an infection with SARS-CoV-2 in the previous month. On the second day of hospitalisation, he presented precordial and abdominal pain and bilateral non-exudative conjunctivitis with worsening of the macular rash on the forearms and lower limbs. The patient was clinically stable with normal electrocardiogram, but in the next hours, sudden and progressive deterioration with tachycardia (130 bpm), hypotension (mean arterial pressure 34 mmHg), oliguria (diuresis 0.7 mL/kg/h) and hypoxaemia (Peripheral oxygen saturation (SpO_2) 93%) was noted. Computed tomography angiography of the chest reported moderate COVID pneumonia and excluded pulmonary thromboembolism, and abdominal computed tomography described mesenteric lymphadenitis. Laboratory results showed increased inflammatory markers: C-reactive protein 262 mg/dL, procalcitonin 0.91 ng/dL, erythrocyte sedimentation rate 58 mm/h, lymphopenia 630 lymph/mm^3, ferritin 309 ng/mL, interleukin (IL)-6 456.70 pg/mL and serum protein amyloid A 1140 mg/L. The patient rapidly evolved to renal failure (Glomerular filtration rate (GFR) 63 mL/min/1.73 m^2) and cardiac lesion (Table 1). Admitted to the PICU, volume challenge was performed without response, starting dopamine (8 µg/kg/min) and noradrenaline (0.4 µg/kg/min). In the setting of significant hypoxaemia with increased inspiratory oxygen fractions and decreased level of consciousness, mechanical ventilation was required. Echocardiogram showed left ventricle fractional shortening of 25% without focal wall motion abnormalities or coronary arteries involvement. Pro-BNP reached a maximum value of 564 pg/mL, Creatine kinase muscle and brain (CK MB) 8.8 ng/mL and troponin 4633 pg/mL (Fig. 1).

PCR for SARS-CoV-2 in naso/oropharyngeal swab, aspirate of oropharyngeal secretions and trachea resulted negative but serology was IgG positive. He was treated with 1 g/kg/dose IVIG daily for 2 days and methylprednisolone 40 mg/dose, twice daily for 5 days. He was also medicated with hydroxychloroquine (HCQ) for 5 days (6.5 mg/kg/dose on the first day posteriorly 3.25 mg/kg/dose, twice daily) without complications and prophylactic enoxaparin. In parallel, he was under a 14-day course of intravenous vancomycin, ceftriaxone and clindamycin.

Table 1 Laboratory data at the admission to Pediatric intensive care unit (PICU) and maximum altered values during hospitalisation

	PICU admission values	Maximum altered values	Institutional normal range
Haemoglobin (g/dL)	11.8	11.8	13.0–16.0
White blood cells ($\times 10^9$/L)	9.83	19.17	4.5–13.0
Neutrophils ($\times 10^9$/L)	8.77	17.95	4.5–13.0
Lymphocytes ($\times 10^9$/L)	0.63	0.61	1.0–5.3
Platelets ($\times 10^9$/L)	195	183	150–450
Fibrinogen (g/L)	4.3	5.8	1.54–4.88
International normalised ratio	1.30	1.68	0.93–1.10
D-Dimers (μg/L)	2123	2123	<230
Blood urea nitrogen (mg/dL)	38	46	10.8–38.4
Creatinine (mg/dL)	1.08	1.08	0.57–0.80
C-reactive protein (mg/L)	292.9	399.3	<5.0
Procalcitonin (ng/dL)	0.95	1.10	<0.06
Erythrocyte sedimentation rate (mm/h)	40	58	<11
Creatine kinase (U/L)	153	180	30–200
Ferritin (ng/mL)	332.1	426.3	13.70–78.80
Lactate dehydrogenase (U/L)	315	315	157–272
Interleukin-6 (pg/mL)	456.70	456.70	<4
Troponin-I (pg/mL)	4632	4632	<34.2
Pro-BNP (pg/mL)	466	564	<100
Triglycerides (mg/dL)	256	95	<150

BNP, Brain natriuretic peptide.

Evolution was positive (Fig. 1) with apyrexia since day 2 of therapy, vasopressor support suspended on day 5 and extubated after 6 days. A weight loss of 10 kg was present during discharge, after 19 days of hospitalisation. Paediatric cardiology reassessment had no electrocardiographic or echocardiographic alterations: fractional shortening was 35.7%. A month after discharge cardiac Magnetic resonance (MR) showed a small area of myocardial fibrosis, normal cardiac volumes and systolic function.

Discussion

The initial cases of MIS-C had an inflammatory syndrome that simulated Kawasaki Disease (KD). However, as more children were reported, it was found that the phenotype was more heterogeneous, more like a variation of toxic shock syndrome and less like classic KD.[2]

The clinical picture of MIS-C has some characteristics of the classic KD, such as mucocutaneous involvement, as in our patient, but gastrointestinal symptoms are more frequent such as diarrhoea, vomiting and abdominal pain associated with mesenteric lymphadenitis. In KD, changes in coronary arteries are frequent but in MIS-C, myocardial involvement appears to be central to the severity of the disease and consequence of systemic hyper-inflammation, along with the dysfunction of other organs. In our case, the extent of the myocardial injury was not only evident by the significant elevation of cardiac injury markers, but also by the evidence of decreased cardiac function. Elevation of troponin is an important marker of prognosis and should be seen as a warning sign even if not generally increased at the beginning of hospitalisation.[3] Interestingly, what we see in this case is that, simultaneously with an initial decrease in troponin in the acute phase, there was a transient increase in BNP. BNP is a quantitative biomarker of haemodynamic myocardial stress and heart failure that is frequently elevated among patients with severe inflammatory and/or respiratory illnesses.[4] The experience in patients with COVID-19 is limited and the experience with patients post-SARS-COV-2 infection is lesser but should be seen in this range of age and in a previously healthy adolescent as a reflection of the acute haemodynamic stress related to the inflammatory status, particularly with the extent of right ventricular haemodynamic stress, and possibly constitute a relevant marker to include in the risk stratification of these patients.

Overproduction of pro-inflammatory cytokines with an early response leads to an increased risk of vascular hyperpermeability, multiple organ failure and, eventually, death.[5]

The most common cause of vasoplegia is sepsis, but it can also occur in the absence of bacterial infection, with systemic inflammation predisposing to organ dysfunction.[6] The vasopressor support in the studies varied from noradrenaline, adrenaline, dopamine, milrinone and vasopressin. In our experience, support with dopamine and noradrenaline was necessary for 5 days. IL-6 also plays a role in haemodynamic deterioration with changes in cardiomyocytes, cardiac fibroblasts and activation of macrophages, the main cells of IL-6 production.[7] The increased levels of IL-6, negative PCR for SARS-CoV-2 and positive IgG serology suggest an immunological mechanism for cardiac injury and vasoplegia in our patient. In the literature, treatment focuses on the modulation of inflammation, with steroids such as methylprednisolone (2 mg/kg/day) and IVIG (2 g/kg).[8] Other immunomodulators have been reserved for steroid and IVIG non-responders such as anakinra or tocilizumab. The therapy proposed for the MIS-C differs significantly between institutions, and the

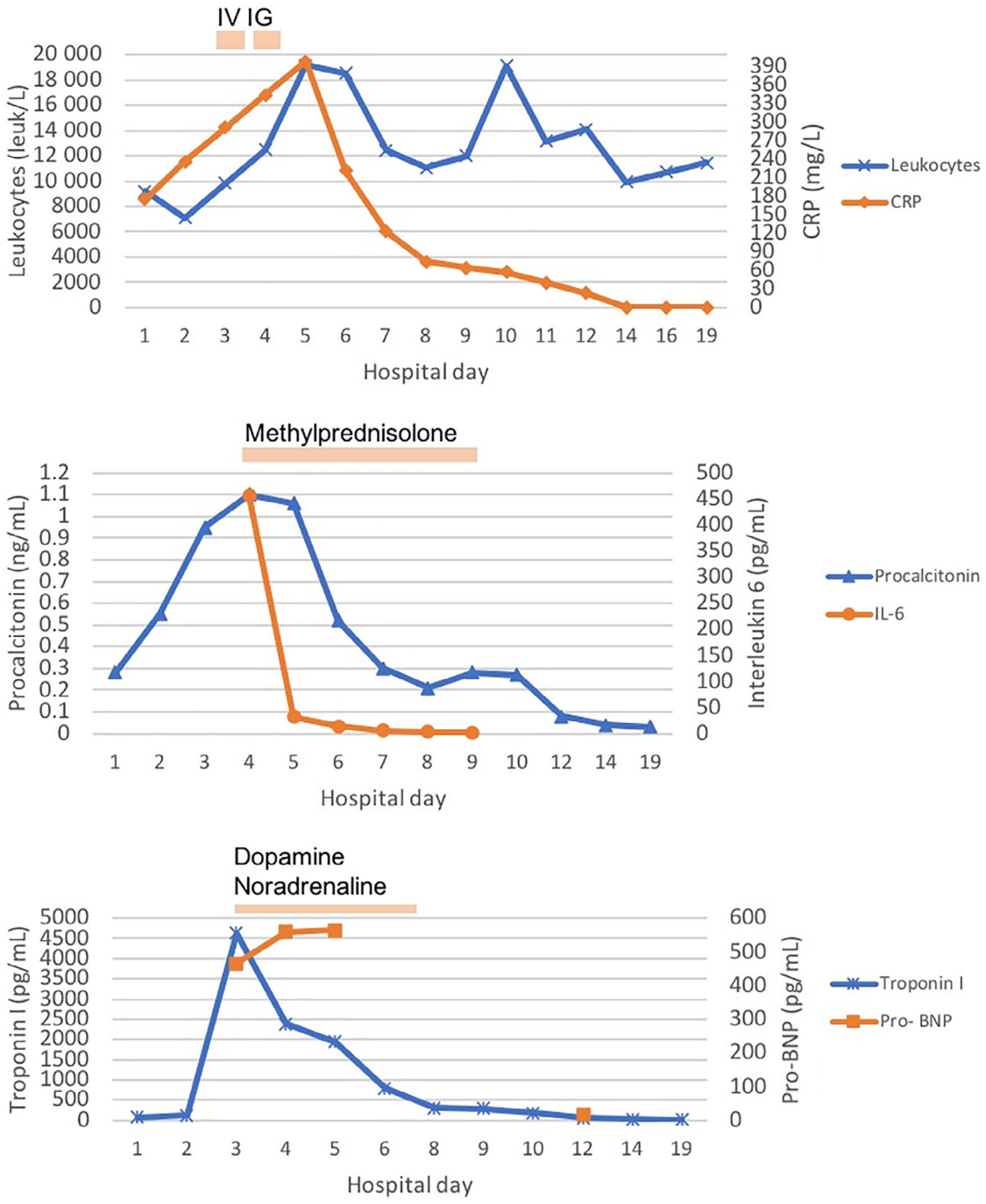

Fig. 1 Variations in laboratory values and relationship with the therapies performed.

particularities of each child's clinical course must be considered in partnership with consultancy specialists. Hennon *et al.* in New York suggested empirical coverage of broad-spectrum antibiotics in patients with MIS-C, as the symptoms overlap with serious bacterial infections, as happened with our patient.[9]

HCQ treatment remains controversial, its potential immunomodulatory effects on several cytokines including IL-1 and IL-6 and *in vitro* activity against SARS-CoV-2 made this drug part of the experimental therapies proposed for COVID-19 and suitable for the management of the inflammatory response in MIS-C.[10] After stopping enrolment in the studies to review safety concerns about the drug, the World Health Organization is resuming a clinical trial that explores whether it can effectively treat COVID-19. However, in our hospital, an observational retrospective study of the treatment of COVID-19 Portuguese paediatric patients with HCQ was conducted, applying a protocol for monitoring cardiac

toxicity. Of the total 14 patients, only 2 temporarily discontinued treatment due to corrected QT Interval (QTc) prolongation (>500 ms), all patients completed the whole treatment and no other side effects or deaths occurred (I Hormigo *et al.*, unpubl. data, 2020).

Endothelial injury and activation of coagulation have been associated with an increased risk of thromboembolic events in patients with COVID-19; following the recommendations of the literature, prophylactic anticoagulation should be administered to critically ill patients.[11,12]

The follow-up of our patient included reassessment with an echocardiogram, showing no abnormalities (including coronary arteries) and cardiac MR with a small area of myocardial fibrosis, without evidence of loss of function. Other follow-up visits are recommended, depending on the course of the disease and, in our particular case, including visits for physical and respiratory rehabilitation and nutrition.

This is the first case of MIS-C described in Portugal. Within the heterogeneous phenotype of the disease, our case presented itself in a particular way, with distributive shock and a component of vasoplegia. The pathophysiology of vasoplegic shock and cardiac dysfunction of this syndrome depends on the host's intrinsic immunological factors that promote an inadequate immunomodulatory response. All of these elements support the need to use appropriate anti-inflammatory and vasopressor strategies.

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You are my Sunshine by Tarlia McGlashan (age 10) from Operation Art 2021