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Immune and coagulation profiles in adults with multisystem inflammatory syndrome: A brief report of 3 patients

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ABSTRACT

Introduction: There is a paucity of information on the cytokine, complement, endothelial activation, and coagulation profiles of multisystem inflammatory syndrome in adults (MIS-A), a rare but serious complication following recovery from SARS-CoV-2 infection. We aim to examine the immune biomarker and coagulation profiles in association with the clinical presentation and course of MIS-A.

Method: The clinical features of MIS-A patients admitted to our tertiary hospital were documented. Their levels of interleukin (IL)-1β, IL-6, IL-10, IL-17, IL-18, interferon-α (IFN-α), IFN-γ, interferon gamma-induced protein 10 (IP-10), tumour necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1, complement activation product (complement 5a [C5a]), and endothelial biomarker intercellular adhesion molecule-1 (ICAM-1) levels were assayed. The haemostatic profile was assessed with standard coagulation testing and thromboelastography.

Results: Three male patients were diagnosed with MIS-A at our centre from January to June 2022 with a median age of 55 years. All had tested positive for SARS-CoV-2 12–62 days prior to MIS-A presentation, with gastrointestinal and cardiovascular systems as the most commonly involved. Levels of IL-6, IL-10, IL-18, IP-10 and MCP-1 were raised whereas IL-1β, IFN-α, IFN-γ, IL-17 and TNF-α remained normal. Markedly elevated levels of C-reactive protein (CRP), ferritin and ICAM-1 were present in all. C5a was elevated in 2 patients. A hypercoagulable state was demonstrated by raised levels of D-dimer, factor VIII, von Willebrand factor antigen, and ristocetin cofactor with corresponding raised parameters in thromboelastography in the 2 patients who had their coagulation profile assessed.

Conclusion: MIS-A patients demonstrate activation of pro-inflammatory cytokines, endotheliopathy, complement hyperactivation and hypercoagulability.

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Keywords: COVID-19, cytokines, hypercoagulability, hyperinflammatory syndrome

INTRODUCTION

A spectrum of immune dysregulation has been described following SARS-CoV-2 infections—from the cytokine storm in the acute phase, to hyperinflammatory syndromes that occur after the resolution of the initial infection.[1] Multisystem inflammatory syndrome (MIS) was first reported in children in April 2020 as a hyperinflammatory syndrome with features similar to Kawasaki disease and toxic shock syndrome,[2] and is increasingly being recognised in adult patients. MIS is defined as a potentially life-threatening hyperinflammatory state with multiorgan dysfunction that develops after SARS-CoV-2 infection. Following the recognition of multisystem inflammatory syndrome in children (MIS-C), similar presentations in adults were described by the US Centers for Disease Control and Prevention (CDC), which considers patients aged 21 years and above to have MIS in adults (MIS-A).[3] In contrast to MIS-C, MIS-A appears to have a lower incidence of coronary artery aneurysm development but higher

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CLINICAL IMPACT

What is New

- This study evaluates the immune biomarkers and coagulation profiles of adults with multisystem inflammatory syndrome (MIS), data on which are currently lacking.
- In contrast to MIS in children, interleukin (IL)-1β, IL-17, interferon (IFN)-γ and IFN-α remain unaffected in MIS in adults.

Clinical Implications

- The difference in cytokine profiles could have potential implications on the choice of biologic agents for adult MIS patients, as infliximab and anakinra are currently recommended for the treatment of refractory MIS in children.
- Elevated intercellular adhesion molecule-1 and complement 5a may present new insight into the pathogenesis of MIS in adults.

mortality.[4] It is postulated that MIS results from a dysregulated immune response to the virus, although the exact mechanisms by which this response is triggered remain unknown. Formation of autoantibodies, antibody recognition of persistent viral antigens on infected cells, and hyperinflammatory response due to the viral super antigens have been put forth as possible pathophysiological mechanisms. Higher levels of pro-inflammatory cytokines including interleukin (IL)-1β, IL-10, IL-17, IL-18, interferon gamma (IFN-γ), interferon gamma-induced protein 10 (IP-10), and tumour necrosis factor (TNF)-α have been demonstrated in patients with MIS-C compared to those with SARS-CoV-2.[5-7] While the clinical characteristics, presentation and treatment of this novel syndrome have been reported,[3,8,9] there is a paucity of data on the cytokine profile, complement levels, and coagulation profile in MIS-A. Here we describe 3 cases of MIS-A diagnosed and treated at our centre from January to June 2022 where we examined their underlying inflammatory milieu and haemostatic profiles associated with their clinical features.

METHOD

The diagnosis of MIS-A was based on the described clinical presentation in temporal relation to the SARS-CoV-2 infection, with other causes excluded. Blood samples were drawn 12, 29 and 11 days from the onset of MIS in patients 1, 2 and 3, respectively. These samples were drawn on the day or 1 day after our department (Rheumatology, Allergy and Immunology) was consulted. Follow-up testing was done 10–12 weeks after the onset of the illness. Serum cytokine and inflammatory biomarkers including levels of IL-1β, IL-6, IL-10, IL-17, IL-18, IP-10, IFN-γ, IFN-α, TNF-α, monocyte chemoattractant protein (MCP)-1, complement 5a (C5a), and intercellular adhesion molecule-1 (ICAM-1) were assayed by enzyme-linked immunosorbent assay (ELISA BD Biosciences, San Diego, US; R&D Systems, Abingdon, UK; and Bender Med Systems GmbH, Vienna, Austria) according to the manufacturers' recommendations. The lower limit of detection for IL-1β (0.46pg/mL), IL-6 (0.08pg/mL), IL-10 (0.2pg/mL), IL-17 (<0.9pg/mL), IL-18 (0.5pg/mL), IP-10 (<5pg/mL), IFN- γ and MCP-1 (<2pg/mL) IFN-α (<0.5pg/mL), TNF-α (<0.2pg/mL), C5a (<0.015ng/mL) and ICAM-1 (<0.063ng/mL). These cytokines were chosen based on the pro-inflammatory nature described in either MIS-A or SARS-CoV-2 infection, with IL-10 the exception as an immuno-regulatory cytokine.[1,6,7,10]

Two of the 3 patients had thrombotic risk assessed with standard haemostatic tests, namely prothrombin time, activated thromboplastin time, fibrinogen, D-dimer, anti-thrombin, protein C and S levels, factor V, factor VIII and von Willebrand factor antigen (vWF:Ag) (Diagnostica Stago SAS, Asnières sur Seine Cedex, France) and thromboelastography (TEG) (TEG 6s, Haemonetics Corp, Boston, US). Patient 2 had haemostatic profiling 1 day after intravenous immunoglobulin (IVIG) initiation and 4 days after steroid therapy was started, while patient 3 had haemostatic profiling before IVIG therapy and 3 days after steroid therapy was started. The study was approved by the institutional review board (National Healthcare Group, Domain Specific Review Board reference number: 2012/00917), and written informed consent was obtained from participants.

RESULTS

Patient 1, a previously well 44-year-old Chinese male, was admitted after a syncopal episode 4 weeks after a SARS-CoV-2 upper respiratory tract infection (URTI). Fever, right-sided throat discomfort, vomiting, and diarrhoea were also present on admission. Of interest, this patient had prominent swelling at the right submandibular area. Computed tomography (CT) of the neck showed thickening of the right fossa of the Rosenmüller and lateral oropharyngeal wall. There was fat stranding in the right parapharyngeal space, extending along the right side of the neck down to the supraclavicular fossa. Mild bilateral lower lobe consolidation with small pleural effusions was

demonstrated on the CT scan. He subsequently developed hypotension and myocarditis (depressed ejection fraction [EF] of 45%, raised troponin levels up to 1,863ng/L, and cardiac magnetic resonance imaging [MRI] features of myocarditis), leading to the diagnosis of MIS-A. His fever lysed after the initiation of ibuprofen. The patient was not treated with glucocorticoids as his fever had lysed with non-steroidal anti-inflammatory drugs alone and blood pressure had improved by the time the diagnosis was made. IVIG 2g/kg was administered in view of cardiac dysfunction. Repeat cardiac imaging showed improvement in his EF to 69%.

Patient 2, a 55-year-old Indian male with pre-existing ischaemic heart disease (IHD), mixed cardiomyopathy with a baseline EF of 30%, and dialysis-dependent end-stage kidney disease (ESKD) presented with fever and abdominal pain 8 weeks after a SARS-CoV-2 URTI. He developed recurrent ventricular arrhythmias with cardiovascular collapse not accounted for by coronary angiography findings of a widely patent right coronary artery (RCA) stent with minor coronary artery disease. His EF was stable at 30% on transthoracic echocardiography. A cardiac MRI could not be performed in view of his ESKD. He was treated with IVIG 2g/kg and intravenous (IV) hydrocortisone with good response. An implantable cardioverter defibrillator was inserted prior to discharge. Although the onset of symptoms was 62 days after his SARS-CoV-2 infection, his clinical syndrome was in keeping with MIS-A, having excluded differentials such as infection and malignancy. He had no features of other autoimmune or autoinflammatory diseases. He responded rapidly to IV hydrocortisone and IVIG. He remained well at follow-up 6 months after his illness and 4 months being off glucocorticoids. Singapore MIS-C cases presented 2–8 weeks after the initial COVID-19 infection.[11,12] Rare cases of MIS-C presenting 16 weeks after the initial COVID-19 illness have been described.[13]

Patient 3 is a 58-year-old Chinese male with virologically suppressed human immunodeficiency virus (HIV) and poorly controlled diabetes mellitus (DM). His CD4 prior to admission was 256 cells/μL and CD8 1,075 cells/μL. He presented with 3 days of generalised abdominal pain and vomiting. On day 2 of admission, he developed fever and erythematous blanchable patches over the face and chest, petechial macules over the abdomen, arms, and lower back, with changes of desquamation over the upper back. Subsequently, new-onset atrial fibrillation (AF), hypotension requiring inotropic support, acute renal failure with oliguria, and metabolic acidosis developed. He demonstrated rapid clinical improvement upon initiation of IV hydrocortisone and IVIG. A repeat TEG 5 days after IVIG showed improvement in markers for hypercoagulability (online Supplementary Materials).

Demographics, clinical presentation, laboratory findings, treatment, and outcomes are summarised in Table 1. Increased serum pro-inflammatory cytokines IL-6, IL-10, IL-18, and IP-10, together with C-reactive protein (CRP), ferritin, and ICAM-1 were observed in all 3 patients, while levels of IL-1β, TNF-α, IFN-γ, IFN- α, and IL-17 were normal. LDH, C5a and MCP-1 levels were elevated in 2 patients. Raised levels of D-dimer, factor VIII, vWF:Ag, and ristocetin cofactor were found in the 2 patients who had their coagulation profile assessed. Hypercoagulability was demonstrated in these 2 patients. Prothrombin time and activated thromboplastin values were normal. Platelet counts were elevated in 2 of the 3 patients. It is of interest that in Patient 1 and Patient 2, ferritin, IL-18 and IP-10 levels decreased but remained elevated after 10–12 weeks in the subsequent follow-up study, suggesting these inflammatory cytokines may still be active. These levels returned to the normal range for Patient 3.

DISCUSSION

MIS-A is a rare complication following recovery from a SARS-CoV-2 infection. A systemic review of 221 patients reported that 57% of patients required intensive care unit (ICU) admission, with a mortality rate of 7%.[8] Given the severity of this illness and the availability of therapeutic options, early recognition is important to guide the management.

The most common findings in MIS-A are fever, and haematologic, cardiovascular and gastrointestinal involvement;[8] however, atypical manifestations are being increasingly recognised. Our patient 1 had parapharyngeal oedema which had been described previously only in MIS-C.[14]

Cytokines play an important role in understanding pathogenesis and may help guide the treatment with biologic agents. Similar to the profiles found in paediatric patients, our patients demonstrated elevated levels of IL-6, IL-10, IP-10, IL-18 and MCP-1. Interestingly, while patients with MIS-C have been reported to have elevated IL-1β, IL-17, IFN-α, IFN-γ and TNF-α levels,[15,16] all of our patients demonstrated normal levels of these cytokines. While infliximab and anakinra are currently recommended for the treatment of refractory MIS-C,[17,18] our finding of normal TNF-α

Table 1. Demographics, clinical presentation, laboratory findings, treatment and outcomes of multisystem inflammatory syndrome in adult (MIS-A) patients

		Patient 1	Patient 2	Patient 3
Demographics				
Age, years, male sex		44	55	58
Ethnicity		Chinese	Indian	Chinese
Medical history		None	ESKD, IHD, mixed cardiomyopathy	HIV (on RAL + 3TC + ATV), poorly controlled DM (receiving metformin 850mg BD and linagliptin 5mg OM)
Clinical presentation				
Onset after SARS-CoV-2 infection, days		29	62	12
Duration of symptom onset to admission, days		4	2	2
Initial symptoms		Fever, right-sided throat pain, syncope, vomiting, diarrhoea	Fever, abdominal pain	Abdominal pain, vomiting
Maximal temperature, °C		40.8	39	39
Clinical features		Fever, cardiomyopathy, hypotension, gastrointestinal (vomiting)	Fever, recurrent VT/VF collapse, hypotension, gastrointestinal (nausea, abdominal pain)	Fever, hypotension, AF, rash, gastrointestinal (vomiting, abdominal pain), acute kidney injury
Investigations				
Laboratory tests	(Healthy reference)			
SARS-CoV-2 infection confirmed by		ART and RT-PCR (cycle threshold 16.23)	ART	ART
Range of leucocyte count during hospitalisation, $x10^9$/L	4.0–9.6	7.0–23.4	7.5–17.0	10.3–18.3
Leucocyte count corresponding to follow-up immunological profile, $x10^9$/L[a]		4.8	7.8	11.2
Range of lymphocyte count during hospitalisation, $x10^9$/L	1.10–6.60	0.44–2.02	0.36–3.84	0.45–4.65
Range of platelet count during hospitalisation, $x10^9$/L	150–360	172–1177	145–397	191–289
Platelet count corresponding to follow-up immunological profile, $x10^9$/L[a]		306	311	245
Peak CRP, mg/L	<5	>380	131.1	229.5
CRP corresponding to follow-up immunological profile, mg/L[a]		2.8	21.9	5.4
Peak ferritin, µg/L	12–307	5367	4175	669
Ferritin corresponding to follow-up immunological profile, µg/L[a]		704	613	22
LDH, U/L	270–550	448	1092	813

Table 1. Demographics, clinical presentation, laboratory findings, treatment and outcomes of multisystem inflammatory syndrome in adult (MIS-A) patients (Cont'd)

		Patient 1	Patient 2	Patient 3
Immunological profile				
Timing of initial test from onset of illness		12 days	29 days	11 days
IL-6, pg/mL	<2	74.1	177.8	109.6
IL-6 follow-up,[a] pg/mL		1.1	2.3	0.3
IL-10, pg/mL	<2	27.6	47.5	2.9
IL-10 follow-up,[a] pg/mL		1.9	1	1.2
IP-10, pg/mL	31.9 (23.2–42.6)[b]	3848.7	225	1989.9
IP-10 follow-up,[a] pg/mL		102.6	124.3	77.6
IL-18, pg/mL	138 (107–169)[b]	2601.9	1922.4	1360.1
IL-18 follow-up,[a] pg/mL		204.3	417.1	95.4
C5a, ng/mL	47.4 (32.1–53.4)[b]	79.91	111.4	28.5
C5a follow-up,[a] ng/mL		32.6	42	29.5
ICAM-1, ng/mL	<95	187.8	355.9	231.1
ICAM-1 follow-up,[a] ng/mL		52.9	76.4	42.7
MCP-1, pg/mL	168.2 (134.2–196.6)[b]	380.7	1748.7	135.8
MCP-1 follow-up,[a] pg/mL		163.3	123.9	125.7
Coagulation studies				
Prothrombin time, seconds	11.7–14.0	16.1	17.8	12.5
Activated partial thromboplastin clotting time, seconds	27.0–27.0	49.2	33.1	34.2
Thrombin clotting time, seconds	15.0–18.0	N/A	15.9	17.4
D-dimer, µg/mL	<0.50	N/A	>4	>4
Fibrinogen, g/L	1.8–4.5	N/A	2.8	6.2
Anti-thrombin (%)	80–130	N/A	65	81
Protein S activity (%)	65–130	N/A	70	81
Protein C activity (%)	70–150	N/A	63	76
Factor V (%)	70–120	N/A	43	116
Factor VIII (%)	60–150	N/A	325	304
vWF:Ag (%)	56–160	N/A	>400	280
Ristocetin cofactor	47–148	N/A	>240	240
Cardiac investigations				
Transthoracic echocardiogram		EF 45%, mild global hypokinesia	EF 30%, regional wall motion abnormality consistent with multivessel disease	EF 60%, no RWMA or significant valvular dysfunction[c]
Others		CMR features met criteria for acute myocarditis	Coronary angiogram: patent RCA stent, minor coronary artery disease	N/A

Table 1. Demographics, clinical presentation, laboratory findings, treatment and outcomes of multisystem inflammatory syndrome in adult (MIS-A) patients (Cont'd)

	Patient 1	Patient 2	Patient 3
Treatment			
High dependency or intensive care unit care	Yes	Yes	Yes
Inotrope or vasopressor use	Yes	Yes	Yes
Steroid use	No	Yes	Yes
Steroid regime	N/A	IV hydrocortisone 50mg Q6H (6 days) → IV hydrocortisone 50mg Q8H (4 days) → prednisolone 30mg OM (1 week) → prednisolone 20mg OM (2 weeks) → then tapered by 5mg each week.	IV hydrocortisone 50mg Q6H (1 week) → prednisolone 50mg (1mg/kg, 4 days) → 40mg (12 days) → 30mg (2 weeks) → then tapered by 5mg every 2 weeks.
IVIG	Yes	Yes	Yes
Anticoagulation	No	No	Yes
Others	Ibuprofen		
Outcome			
Length of hospital stay, days	17	33	16
Outcome	Discharged	Discharged	Discharged

3TC: lamivudine; AF: atrial fibrillation; ART: antigen rapid test; ATV: atazanavir; BD: twice daily; CMR: cardiac magnetic resonance imaging; CRP: C-reactive protein; C5a: complement 5a; DM: diabetes mellitus; EF: ejection fraction; ESKD: end-stage kidney disease; HIV: human immunodeficiency virus; ICAM-1: intracellular adhesion molecule-1; IFN: interferon; IHD: ischaemic heart disease; IL: interleukin; IP-10: interferon gamma-induced protein; IV: intravenous; IVIG: intravenous immunoglobulin; LDH: lactate dehydrogenase; MCP: monocyte chemoattractant protein; N/A: not applicable; OM: every morning; RAL: raltegravir; RCA: right coronary artery; RT-PCR: reverse transcription polymerase chain reaction; RWMA: regional wall motion abnormality; TNF: tumour necrosis factor; VF: ventricular fibrillation; VT: ventricular tachycardia; vWF Ag: von Willebrand factor antigen

[a] C-reactive protein, ferritin, leucocyte and platelet counts and cytokine analysis 10–12 weeks post MIS-A diagnosis

[b] Mean (95% range)

[c] Imaging was performed 2 weeks after admission

and IL-1β levels could have potential implications on the choice of biologic agents for adult MIS patients. Further studies are required to determine if this is a common feature of MIS-A.

Robust type 1 IFN gene signalling pathways and TNF-α/IL-1 have been implicated in the cytokine storm and hyperinflammation of severe SARS-CoV-2 infections.[19] The lack of IFN-α, TNF-α and IL-1β in our MIS-A patients point to a potentially different immune-dysregulation from the SARS-CoV-2 infection.

IP-10 has been suggested as a potential biomarker to predict left ventricular dysfunction in MIS-C patients.[20] Our MIS-A patients, all with cardiovascular manifestations, demonstrated elevated IP-10 levels. Patient 3's echocardiogram was performed 2 weeks after admission and administration of corticosteroids and IVIG, and it is possible that his cardiac function had improved by the time his cardiac imaging was performed.

C5a has been implicated in severe pneumonia, acute respiratory distress syndrome, and SARS-CoV-2-related manifestations, including heart, kidney and endothelial dysfunction. As the complement system is the link between innate immunity and coagulation, its overactivation could promote thrombotic events in patients with severe SARS-CoV-2 infection.[21] Our first 2 patients demonstrated elevated levels of C5a while the normal level in patient 3 could be the result of the test being drawn after 3 days of IV hydrocortisone.

ICAM-1 is a cell surface glycoprotein and an adhesion receptor regulating leukocyte recruitment from the circulation to sites of inflammation,[22] and its endothelial expression is increased in patients with severe SARS-CoV-2 infection. This increased expression of ICAM-1

may lead to a sustained pro-inflammatory state, resulting in systemic endothelial dysfunction.[23] To our knowledge, this is the first study assessing ICAM-1 in MIS-A patients.

Increased risks of thromboembolic events have been reported in patients with MIS-C;[24] risk factors include central venous catheterisation, age ≥12 years, malignancy, ICU admission, and elevated D-dimer levels >5 times the upper limit of normal.[24] The American College of Rheumatology recommends that anticoagulation should be considered on an individual basis, with stronger recommendations for paediatric patients with coronary artery aneurysms (z-score ≥10.0), EF <35%, and those with documented thrombosis.[17] At present, information on the thrombotic and bleeding risks in the adult population remains unclear. Haemostatic profiling of Patient 2 was performed on Day 5 of IV hydrocortisone and Day 2 of IVIG. While he did demonstrate features of hypercoagulability (shown by raised levels of factor VIII, vWF:Ag, ristocetin cofactor and D-dimer, and depressed levels of anti-thrombin III and protein C), the TEG did not show features of hypercoagulability. This is most likely due to the effect of immunosuppression. As Patient 2 was at increased risk of bleeding from ESRD and also because of the rapid clinical improvement with IVIG and IV hydrocortisone, thromboprophylaxis was not administered. Assessment of the haemostatic profile in Patient 3 was performed on Day 4 of IV hydrocortisone, and before IVIG was initiated. He had elevated D-dimer, hyperfibrinogenaemia, factor VIII, and vWF: Ag levels—a profile similar to the hypercoagulability seen in patients with acute SARS-CoV-2 infection. This was supported by hypercoagulable parameters present in the TEG, where there was increased maximal amplitude and raised angle, likely contributed by a hyperfibrinogenaemic state and raised factor VIII levels. Given the hypercoagulable state and a high Padua venous thromboembolism (VTE) score, he was started on thromboprophylaxis with subcutaneous heparin and later anticoagulation with dabigatran, as he had concomitant AF. Repeat TEG performed 8 days post-IV hydrocortisone and 5 days after IVIG showed marked improvement in the hypercoagulability. Mechanisms for hypercoagulability in SARS-CoV-2 survivors have been largely focused on endothelial dysfunction and hyperinflammation as the primary mechanism,[25] where the prior cytotoxic effects of SARS-CoV-2 virus results in an overwhelming immune response causing damaged endothelium, exposed tissue factor and procoagulant cytokines, culminating in secondary hypercoagulability. While none of our patients developed thromboembolic events during their hospitalisation, a hypercoagulable state was observed in the 2 patients profiled. Thus a combination of haemostatic profiling and the use of thrombotic risk assessment models—such as IMPROVE-DD VTE or Padua VTE risk scoring—while yet to be clinically validated in critically ill patients with MIS-A, should be considered to guide decisions on thromboprophylaxis.

Treatment of MIS-A is drawn from experience in the management of MIS-C. First-line treatment usually includes the immunomodulator IVIG and glucocorticoids. The mechanism of action of IVIG includes inhibition of complement deposition, enhancement of regulatory T cells, and accelerated clearance of autoantibodies.[26] Proposed immunologic mechanisms of MIS include: superantigen-like activation of the immune system; and autoantibody production resulting in activation of Fcγ receptors on neutrophils and macrophages, causing secretion of pro-inflammatory cytokines.[27] IVIG-mediated neutralisation and clearance of autoantibodies may explain IVIG efficacy in MIS. In patients with refractory disease, pulse methylprednisolone, and/or biologics such as anakinra and infliximab may be considered. While Patients 2 and 3 had good treatment responses with IVIG and IV hydrocortisone, Patient 1 responded to IVIG alone. The dramatic improvement in his clinical, laboratory markers, and recovery of his EF within a week without the use of corticosteroid is noteworthy. Further studies on the immunopathogenesis and biomarkers related to MIS-A is required, as our preliminary findings demonstrate a cytokine profile different from that of MIS-C.

CONCLUSION

MIS-A patients demonstrate activation of pro-inflammatory cytokines, endotheliopathy, complement hyperactivation and hypercoagulability. In contrast to MIS-C, IL-1β, IL-17, IFN-γ and IFN-α remain unaffected. This could have potential implications on the choice of biologic agents for adult MIS patients as infliximab and anakinra are currently recommended for the treatment of refractory MIS-C.

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