Delayed-Onset Myocarditis following COVID-19:

A Post-Infectious Multisystem Inflammatory Syndrome in Adults with Severe but Reversible Cardiac Injury

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A multisystem inflammatory syndrome (MIS) occurring several weeks after SARS-CoV-2 infection and that can include severe acute heart failure was recently reported in children (MIS-C).[1, 2] In adults with acute severe heart failure, we have identified a similar syndrome and describe presenting characteristics, diagnostic features and early outcomes. Our data also complement recently presented reports of MIS syndromes in adults (MIS-A).[3]

The recognition that three patients presenting with fulminant myocarditis also had clinical features of COVID19 but were negative for SARS-CoV-2 RT-PCR, was made during recruitment for a study of cardiac injury associated with SARS-CoV-2. To identify implications for patient care, we audited digital records to identify similar presentations to Barts Health NHS Trust and Guy's and St Thomas' NHS Trust between March and September 2020. Formal ethics approval was not required. All cases had stored serum for antibody testing, and included 9 'Subjects' (cases 1-9) with (i) acute cardiac decompensation, (ii) negative RT-PCR for SARS-CoV-2, (iii) markedly elevated serum troponin, and (iv) significantly raised inflammatory markers. We also studied 3 'Controls' (cases 10-12) with acute heart failure and SARS-CoV-2 antibodies, but without all the other features.

Subjects were more often male (7/9), of Black African ancestry (7/9), and mean age was 36 years (23-53). Both female Subjects (cases 9,11) presented during or shortly after pregnancy, one of whom had gestational diabetes. One male case included significant co-morbidity (case 4, hypertension secondary to primary hyperaldosteronism).

Presenting features in Subjects included febrile illness (all, 1–7 days), dyspnoea (5/9), gastrointestinal involvement (pain, diarrhoea or vomiting in 8/9, with imaging evidence of enteritis in 3/8), pulmonary infiltrates (8/9), and muco-cutaneous involvement (4/9). A recent history of typical COVID19 symptoms followed by recovery was present in 4/9, and included RT-PCR proven infection in one. Subjects had multiple negative SARS-CoV-2 RT-PCRs during their cardiac admission (4·6 tests, range 3-8). SARS-CoV-2 antibody testing on stored serum taken 4.2 days (0-20) after admission was positive in 7/9. Elevated C-reactive protein (CRP, 38-89 times upper limit of normal [ULN]), ferritin (0·2-16

ULN), neutrophils (1·5-6·6 ULN), and neutrophil:lymphocyte ratio (4·5-42) were striking (Figure 1, appendix).

Subjects deteriorated rapidly after admission, including eight transferring into tertiary cardiac intensive care (ICU) 2.9 days after admission (1-6 days); one Subject (case 5) was transferred to the local ICU one day after admission. Therapies included pharmacological (8/9) and mechanical (2/9) circulatory support. Corticosteroids (6/9) with or without intravenous immunoglobulin (IVIG, 2/6) were given frequently, as were broad spectrum antimicrobials (7/9). One Subject received anakinra.

Severe left ventricular (LV) systolic impairment (Figure 1) was present on admission echocardiography with ejection fraction (LVEF) 24% (10-35%). Peak troponin ranged between 6-208 ULN, and alongside inflammatory markers and clinical status demonstrated rapid improvement following ICU admission and therapy (Figure 1). The average length of ICU stay was nine days (2-25 days).

Acute cardiac MRI (CMR1), available for all Subjects 11 days (3-24) following ICU admission, demonstrated LVEF 57% (42-70%). Late gadolinium enhancement (LGE, 6/9), elevated T1 (7/7), and elevated T2 (6/9) were present in most Subjects (Figure 1). Convalescent CMR (CMR2) in six Subjects 103 days (48-155) following CMR1 detected normal LVEF (57-70%) in all except case 4, where systolic function again deteriorated. Comparing paired data, LVEF recovered markedly between admission and CMR1 (22% vs. 53%; p=0·00004), but was similar between CMR1 and CMR2 (53% vs. 58%; p=0·42). Abnormal LGE (4/6 to 1/6), T1 (6/6 to 4/6) and T2 (4/5 to 1/5) were less frequent on CMR2 (paired data: T1 1210 to 1044msec, p=0·004; T2 58 to 50msec, p=0·007); T1 and T2 remained elevated in case 4.

We propose that this series describes cardiogenic shock due to a post-COVID19 multisystem inflammatory syndrome in adults (MIS-A). Similarities with MIS-C include frequent GI involvement, pulmonary infiltrates, muco-cutaneous involvement, and significantly elevated inflammatory markers.[1,2] Detectable antibody and RNA absence is consistent with recent recovery following infection

in London naive to SARS-CoV-2 before March 2020. Not all Subjects had detectable SARS-CoV-2 antibody, another feature common to MIS-C, and one with important clinical implications. A preponderance of male and (UK) minority ethnic group patients mark another similarity with MIS-C. As in similar MIS-C cases, a rapid and profound improvement in cardiac function closely followed initiation of supportive, antimicrobial, and/or immunomodulatory therapy.

The three Controls (cases 10-12) help define the key features of cardiogenic shock in MIS-A, and illustrate diagnostic challenges arising from the heterogeneous aetiology of acutely presenting heart failure. Presenting within weeks of SARS-CoV-2 infection, none demonstrated extreme elevations of inflammatory markers, GI symptoms or muco-cutaneous features. Only Control case 12 had very elevated cardiac troponin, and had lymphocytic myocarditis with parvovirus on biopsy. With increasing population seropositivity, the Controls also emphasise that anti-SARS-CoV-2 IgG will make a limited contribution to MIS-A diagnosis.

Our study's limitations include selection bias; notably, lethal and milder cases are not represented. All therapeutic interventions are uncontrolled and causality is not inferred. Two Subjects were negative for SARS-CoV-2 antibody, consistent with seropositivity prevalence in MIS-C. (1,2) This may reflect test sensitivity, failed/delayed seroconversion, and/or early declines in antibody levels. Alternatively, initiating events other than SARS-CoV-2 may be responsible.

However, this communication's primary purpose is to highlight a novel clinical presentation of a multi-system disorder that can have life-threatening features, yet may respond adroitly to therapy. Potential factors responsible for the delay in identifying this syndrome in adults and/or diagnosing individual cases include: 1) severe cardiac involvement is likely to be rare, 2) negative RT-PCR testing at the time of the cardiac presentation, 3) limited diagnostic role for antibody testing: unavailable early in the pandemic, poor specificity subsequently, 4) attribution of systolic impairment to pre-existing cardiac disease, 5) high frequency of COVID19-related acute myocardial injury and multiplicity of its causes: up to 40% of hospitalised patients have elevated troponin[4] and 6) difficulties obtaining

complex/invasive diagnostic investigations in ICU patients during the pandemic. Finally, as MIS-C is a wide-spectrum disorder, including variable severity and involving multiple systems,[2] adult practitioners should also be alert to the likelihood that MIS-A will be heterogenous and may not include cardiac involvement.

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Figure Legend:

Figure 1. Temporal changes in selected markers of systemic inflammation and myocardial damage in Subjects (cases 1-9, solid lines) and Controls (cases 10-12, dotted lines).

A-C: Biochemical markers. Day 0 represents the time-point when corticosteroids were administered, or ICU admission for the cases that did not receive steroids. Data from a prior acute COVID19 admission are available for two cases. (A) Serum Troponin T; (B) Serum ferritin; (C) C-reactive protein.

D-E: Imaging features in Subject cases. Echocardiography was obtained at ICU admission, CMR1 11 days (range 3-24) after ICU admission and CMR2 103 days (48-155) following CMR1. D: For echocardiography, the median value is used whenever EF was reported within a range. E: The highest T1 (left-sided y-axis) and T2 (right-sided y-axis) values reported for each Subject are plotted.

*Subjects 5,8 and 9 and Control 11 did not receive immunomodulatory therapy.

Appendix:

Table 1: Case summaries including Subjects (cases 1-9) and Controls (cases 10-12).

BSA – broad spectrum antibiotics, CMR – cardiac magnetic resonance imaging, CT – computed tomography, CTCA – CT coronary angiogram, CXR – chest x-ray, ECMO – extracorporeal membrane oxygenation as veno-veno (VV) or veno-arterial (VA), EMB – endomyocardial biopsy, ICU - intensive

care unit, LGE – late gadolinium enhancement, LV – left ventricle, PE – pulmonary emboli, PMH – past medical history, TTE – transthoracic echocardiography.

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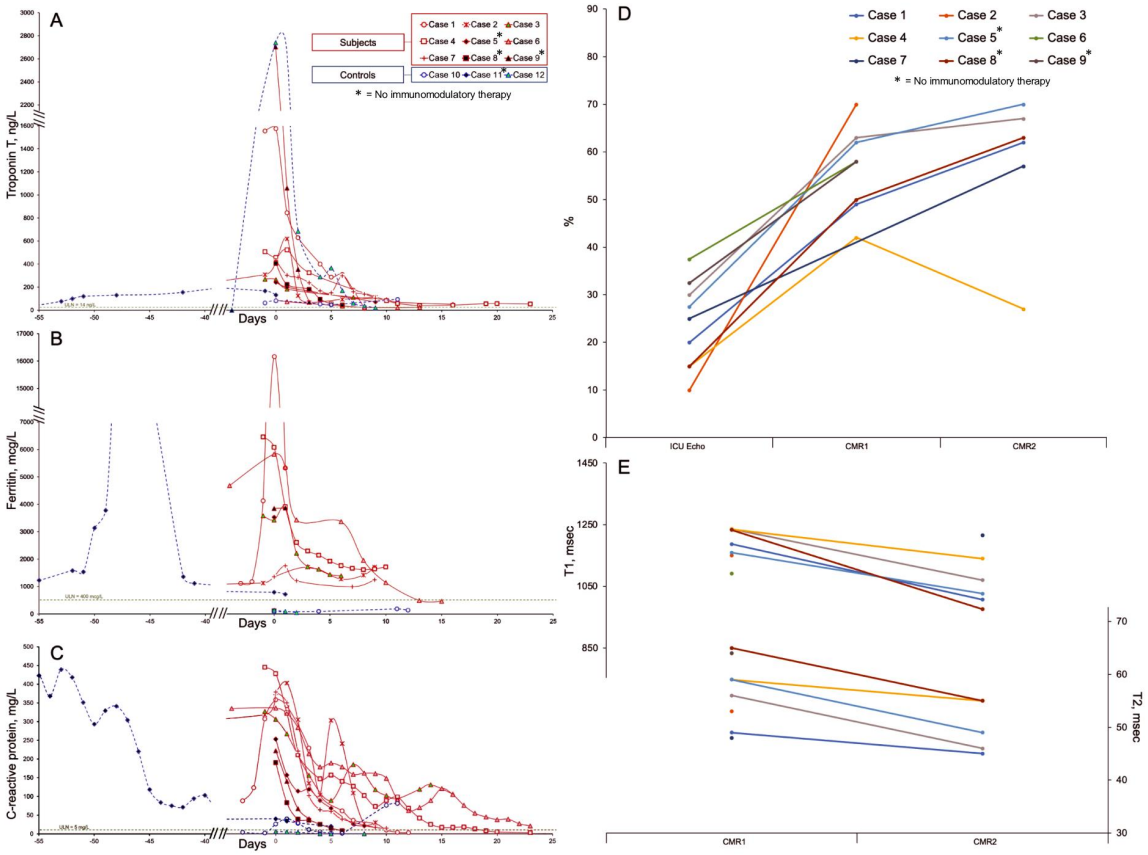
Figure 1.


A
Troponin T, ng/L
Subjects
Controls
Case 1
Case 2
Case 3
Case 4
Case 5*
Case 6
Case 7
Case 8*
Case 9*
Case 10
Case 11*
Case 12
* = No immunomodulatory therapy
Days
B
Ferritin, mcg/L
Days
C
C-reactive protein, mg/L
Days
D
%
Case 1
Case 2
Case 3
Case 4
Case 5*
Case 6
Case 7
Case 8*
Case 9*
* = No immunomodulatory therapy
ICU Echo
CMR1
CMR2
E
T1, msec
T2, msec
CMR1
CMR2

Supplementary Material

Table 1

Age; Gender; Ethnicity; PMH.	Clinical Presentation		ICU Support (length)			Myocardial Imaging		Lab. Results (peak values)	SARS-CoV-2 Results	ICU stay; outcome
	Pre-admission/ Prodrome	Admission to hospital	ICU Referral	Mechanical	Drug Therapy	ICU admission	CMR (when, TnT level)			
Case 1: 42; male; South Asian; no PMH	Fevers, malaise, anosmia and dry cough for 2 weeks followed by 2-month symptom-free interval.	3 days fever, sweats, dizziness, dyspnoea, diarrhoea. Abdominal and palma/plantar rash.	Respiratory failure and cardiogenic shock	Ventilation (24 hrs)	Milrinone, adrenaline; BSA, acyclovir; methylprednisolone	TTE: Bi-ventricular impairment (LVEF 20%). CT: basal consolidation. Angiography: unobstructed coronaries.	Scan 1 (ICU +4days, TnT 630ng/L): LVEF 49%, elevated T1, normal T2, no LGE. Scan 2 (4 months after discharge, TnT 6ng/l): LVEF 62%, normal T1 and T2, no LGE.	CRP 358 mg/L; TnT 1576 ng/L; Ferritin 16154 mcg/L; neutrophils 17x109/l	RT-PCR: 3 x negative; antibody positive	4 days; full recovery
Case 2: 27; male; Black-Caribbean; no PMH	Admission with symptoms, PE, postive RT-PCR and normal TnT. Discharged after 4 days and symptom free for 2 weeks.	4 days abdominal pain, vomiting, fever, chest pain, dyspnoea, sweats	Cardiogenic shock	Ventilation (9 days); VA ECMO (72 hours)	Milrinone, noradrenaline; BSA; methylprednisolone	TTE: Bi-ventricular impairment (LVEF <10%). CT: lung consolidation, duodenitis.	Scan 1 (ICU +14days, TnT 25ng/L): LVEF 70%, elevated T1, normal T2, epicardial LGE.	CRP 403 mg/L; TnT 620 ng/L; Ferritin 1711 mcg/L; neutrophils 11x109/l	RT-PCR: 7 x negative; antibody positive	13 days; full recovery
Case 3: 41; male; Black-African; no PMH	No prodromal symptoms	4 daysfever, dizziness, dyspnoea, abdo pain, diarrhoea	Cardiogenic shock and refractory VF. Brugada-pattern ECG.	Ventilation (48 hrs)	Adrenaline, noradrenaline; BSA; hydrocortisone	TTE: Bi-ventricular impairment (LVEF 30%). CXR: bilateral changes. Angiography: unobstructed coronaries.	Scan 1(ICU + 6days, TnT52ng/l): LVEF63%, elevated T1 and T2, no LGE. Scan 2 (10 weeks after discharge, TnT 8ng/l): LVEF 67%, normal T1, T2, no LGE.	CRP 327 mg/L; TnT 270 ng/L; Ferritin 3893 mcg/L; neutrophils 46.5x109/l	RT-PCR: 4 x negative; antibody positive	4 days; full recovery
Case 4: 53; male; Black-African; hypertension, obesity, chronic kidney disease	Anosmia, myalgia, cold 'like malaria' 3-4 weeks before admission. Partial recovery.	4 days fever, malaise, dyspnoea. Conjunctival keratopathy and tongue changes.	Cardiogenic shock	Ventilation (16 days); VA and VV ECMO 7 days	Adrenaline, vasopressin, milrinone;BSA, oseltamivir; hydrocortisone	TTE: Bi-ventricular impairment (LVEF15%). CXR: bilateral changes.	Scan 1(ICU + 23 days, TnT 54ng/l): LVEF42%, elevated T1 and T2, midwall/epicardial LGE. Scan 2 (5 months after discharge, TnT 49ng/l): LVEF 27%, elevated T1 and T2, midwall/epicardial LGE.	CRP 461 mg/L; TnT 574 ng/L; Ferritin 6461 mcg/L; neutrophils 23x109/l	RT-PCR: 6 x negative; antibody positive	18 days: NYHA2-3
Case 5: 33; male; Black-African; smoker, no other PMH.	No prodromal symptoms	7 days abdominal pain, dyspnoea, diarrhoea and confusion. Skin rash.	Cardiogenic shock	None	Dobutamine, adrenaline; BSA	TTE: Bi-ventricular impairment (LVEF<30%). CT: bilateral lung consolidation and descending/sigmoid colitis	Scan 1(ICU + 10 days, TnT 72ng/l): LVEF62%, elevated T1 and T2, midwall septal LGE. Scan 2 (14 weeks after discharge: LVEF 71%, normal T1 and T2, resolution of LGE.	CRP 253 mg/L; TnT 242 ng/L; Ferritin 3528 mcg/L; neutrophils 34x109/l	RT-PCR: 3 x negative; antibody positive	4 days; full recovery
Case 6: 23; female; Black-African; 8 weeks pregnant.	Sore throat and fevers 6 weeks prior, with complete recovery.	5 days fever, rigors, abdominal pain and PV bleeding. Rash on soles, face and back. Spontaneous abortion.	Cardiogenic shock	Ventilation (15 days)	Noradrenaline, adrenaline, vasopressin, milrinone; BSA; IVIG and hydrocortisone	TTE: Bi-ventricular impairment (LVEF<35%). CT: bilateral lung consolidation and colitis	Scan 1(ICU + 24 days, TnT 34ng/l): LVEF58%, borderline elevated T1, normal T2, no LGE.	CRP 335 mg/L; TnT 90 ng/L; Ferritin 5833 mcg/L; neutrophils 20x109/l	RT-PCR: 8 x negative; antibody positive	25 days: no follow-up data
Case 7: 33; male; Black-Caribbean; no PMH	No prodromal symptoms	4 days myalgia, fevers, headaches and diarhoea	Respiratory failure and cardiogenic shock	Ventilation (4 days)	Milrinone, noradrenaline, levosimendan; BSA; IVIG, anakinra, methylprednisolone	TTE: Bi-ventricular impairment (LVEF 25%). CXR: bilateral lung changes. CTCA normal	Scan 1(ICU + 8 days, TnT 34ng/l): LVEF57%, normal T1 and T2, epicardial LGE.	CRP 379 mg/L; TnT 431 ng/L; Ferritin 1356 mcg/L; neutrophils 20x109/l	RT-PCR: 4 x negative; antibody positive	6 days; full recovery
Case 8: 33; female; South-Asian; gestational diabetes, C-section at 36 weeks gestation.	No prodromal symptoms	Chest pain, dyspnoea, desaturation 24 hours following elective c-section.	Cardiogenic shock	None	Levosimendan	TTE: Bi-ventricular impairment (LVEF <15%). CT: Lung consolidation, no PE. CTCA: no stenoses.	Scan 1(ICU + 3days, TnT ??ng/l): LVEF62%, elevated T1 and T2, extensive midwall and epicardial LGE. Scan 2 (6weeks after discharge): LVEF 63%, normal T1 and T2, resolution of LGE.	CRP 190 mg/L; TnT 406 ng/L; Ferritin 111 mcg/L; neutrophils 13x109/l	RT-PCR: 3 x negative; antibody negative	4 days; full recovery
Case 9: 36; male; Black-African; no PMH	No prodromal symptoms	7-day fever, headache and malaise, 2-days vomiting, upper abdominal pain and loose stools.	Cardiogenic shock	None	None	TTE: Bi-ventricular impairment (LVEF <35%). CXR - subtle bibasal changes	Scan 1(ICU + 4 days): LVEF58%, elevated T2, exrtensive midwall LGE.	CRP 222 mg/L; TnT 2704 ng/L; Ferritin 3847 mcg/L; neutrophils 10x109/l	RT-PCR: 3 x negative; antibody negative	1 day; no follow up data
Case 10: 21; male; Black-African; asthma and family history of dilated cardiomyopathy and premature sudden death	No prodromal symptoms	2-4 weeks dyspnoea, peripheral oedema, chest pain	Cardiogenic shock	None	Milrinone; BSA; methylprednisolone	TTE: Bi-ventricular impairment (LVEF15%). CT: pulmonary oedema +/- consolidation .	No scan obtained. Explant heart: extensive fibrotic changes, no inflammatory infiltrates. Genetic test pending.	CRP 103mg/L; TnT 95 ng/L; Ferritin 182 mcg/L; neutrophils 8x109/l	RT-PCR: 5 x negative; antibody positive	2 days; cardiac transplant 20 days after admissiion
Case 11: 59; male; Black-African; DM II, CKD, obesity, perforated duodenal ulcer	RT-PCR proven COVI19 2 months prior, complicated by perforated ulcer and laparotomy.	3 days dyspnoea, pedal and scrotal oedema	Respiratory failure	None	BSA, oseltamivir	TTE: Bi-ventricular impairment (LVEF<15%). CT: multifocal ground-glass changes.	Scan 1(ICU + 15 days): LVEF16%, mildly elevated T1, normal T2, no LGE.	CRP 34mg/L; TnT 95 ng/L; Ferritin 1074 mcg/L; neutrophils 4x109/l	RT-PCR: 1 x negative; antibody positive	2 days; chronic heart failure symptoms
Case12: 20; female; Black-African; no PMH	No prodromal symptoms	1month chest pain and worsening dyspnoea and orthopnoea	Mobitz 2 AV block, hypotension, monitoring following cardiac biopsy	None	methylprednisolone	TTE: Bi-ventricular impairment (LVEF<45%). CXR: pleural effusions	Scan 1(ICU - 1 day, TnT 2741ng/l): LVEF33%, very elevated T1 and T2, no LGE. Scan 2 (ICU + 6 days, TnT 38ng/l) LVEF 66%, mildly elevated T1 and T2, no LGE. EMB (ICU day 0): lymphocytic myocarditis.	CRP 5mg/L; TnT 2741 ng/L; Ferritin 92 mcg/L; neutrophils 4x109/l	RT-PCR: 3 x negative; antibody positive	1 day; no follow up data