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LETTER TO THE EDITOR

Acute liver and cardiac failure in multisystem inflammatory syndrome in adults after COVID-19

A rapid spread of a novel coronavirus began at the end of 2019 in China. The World Health Organization named the disease COVID-19 [1] and the causative virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

In the early course of the epidemic, it seemed that children do not develop a severe acute illness. However, in the late spring a new multisystem inflammatory syndrome in children (MIS-C) associated with the SARS-CoV-2 infection was described. Most reported cases included characteristics of shock, cardiac dysfunction, gastrointestinal symptoms, substantially elevated inflammatory markers (C-reactive protein (CRP), ferritin, D-dimer, and interleukin-6 (IL-6)), and positive tests for SARS-CoV-2 infection [2]. Possible mechanisms of injury in MIS-C include direct viral tissue damage, endothelial damage and thromboinflammation, dysregulation of immune responses, and maladaptation of ACE2-related pathways [3]. Nowadays MIS-C is considered as a post-infectious complication rather than an active infection.

The clinical presentation of COVID-19 in adults varies extremely. It ranges from asymptomatic cases and mild disease to severe and critical illness. Rare cases of multisystem inflammatory syndrome were also described in adults, forming a so-called multisystem inflammatory syndrome in adults (MIS-A). The current criteria for MIS-A includes: 1) a severe illness requiring hospitalization in a person aged ≥21 years; 2) a positive test result for current or previous SARS-CoV-2 infection (nucleic acid, antigen, or antibody) during admission or in the previous 12 weeks; 3) severe dysfunction of one or more extrapulmonary organ systems (e.g., hypotension or shock, cardiac dysfunction, arterial or venous thrombosis or thromboembolism, or acute liver injury); 4) laboratory evidence of severe inflammation (e.g., elevated CRP, ferritin, D-dimer, or IL - 6); and 5) absence of severe respiratory illness (to exclude patients in which inflammation and organ dysfunction might be attributable simply to tissue hypoxia) [4].

We describe a case of a 22-year-old previously healthy Caucasian male who was admitted to the intensive care unit due to an acute liver and cardiac dysfunction, presenting approximately four weeks after uncomplicated COVID-19 disease. A few days before the hospitalization the patient had fever with chills, headache, sore throat followed by cough due to which the general care physician prescribed azithromycin and amoxicillin. He did not use alcohol, tobacco, or illicit substances.

On examination, the patient was alert and oriented. The temperature was 39 °C, the heart rate 130 beats per minute, the blood pressure RR 95/70 mmHg, the respiratory rate 24 breaths per minute, and the oxygen saturation 90% while the patient was breathing ambient air. Heart examination revealed tachycardia and normal heart sounds. Lung auscultation revealed vesicular breathing. Tenderness in the right upper quadrant of the abdomen was observed accompanied by the enlarged liver.

Polymerase chain reaction SARS-CoV-2 (E gene) was negative and the anti-SARS-CoV-2 antibody test was positive.

During initial observation and treatment in the emergency department, the patient received 1 L of 0.9% saline.

Initial laboratory tests showed increased inflammatory markers, liver and myocardial injury (Table 1). Respiratory insufficiency was present, but of minor relevance.

A chest X-ray revealed bilateral interstitial lesions. Transthoracic echocardiography (TTE) showed biventricular dysfunction; a severely hypocontractile left ventricle with estimated left ventricle ejection fraction (LVEF) of 20–25% and globally reduced right ventricle function (tricuspid annular plane systolic excursion 13 mm).

Based on the clinical presentation and diagnostic work-up a diagnosis of MIS-A was considered. The treatment with furosemide, dobutamine, empiric antibiotic treatment (piperacillin and tazobactam), immune modifying therapy (intravenous immune globulin 2 g/kg iv and methylprednisolone), enoxaparin (0.4 mL s.c.), acetylsalicylic acid 100 mg (ASA), and pantoprazole was initiated. Supplemental oxygen was applied via nasal cannula at a flow rate of 3–4 L/min providing adequate oxygenation. Urine output was 2500 mL after 40 mg of furosemide. Dobutamine was discontinued on the second hospital day. The patient's condition gradually improved.

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Table 1 Laboratory findings.

Variable	Reference range, adults	Hospital day 1	Hospital day 7	7 day after discharge	30 days after discharge
Red cell count (x10^{12}/L)	4.34—5.72	4.38	5.12	4.77	5.12
Hematocrit (%)	41.5—53	34.8	44.6	41.9	43.7
Hemoglobin (g/L)	138—175	123	146	138	150
White cell count (x10^{9}/L)	3.4—9.7	20.2	8.1	9.9	5.8
Differential count (%l)					
Neutrophils	44—72	86	70	54	57.1
Lymphocytes	20—46	6	21	39	29
Monocytes	2—12	2	6	6	11.3
Eosinophils	0—7	0.5	1	0	1.6
Basophils	0—1	0.5	0	0	1
Immature granulocytes	0—2	5	2	1	
Platelet count (x10^{9}/L)	158—424	186	359	361	236
PT	>0.70	0.58	0.81		0.97
Fibrinogen (g/L)	1.8—4.1	>7.0	1.7	2.0	2.5
D dimer (mg/L)	0—0.50	>35.20			
Sodium (mmol/L)	137—146	127	136	140	142
Potassium (mmol/L)	3.5—4.7	3.6	4.6	4.0	4.1
BUN (mmol/L)	2.8—8.3	13.8	7.8	5.1	3.4
Creatinine (μmol/L)	60—104	91	69	65	65
Glucose (mmol/L)	4.2—6.0	6.4		5.5	4.6
Bilirubin (μmol/L)	3—20	27	27	25	24
ALT (U/L)	12—48	1556	503	292	73
AST (U/L)	11—38	381	159	69	32
GGT (U/L)	11—55	37			28
AP (U/L)	60—142	67			67
High sensitive troponin I (ng/L)	0—34.2	446		29	<5
NT-proBNP (ng/L)	<125.0	>35,000	824	341	96
CK (U/L)	0—177	42	16		
LDH (U/L)	<241	383	226		
CRP (mg/L)	<5	239.7	12.4	1.4	1
PCT (μg/L)	<0.25	4.84		<0.06	
IL-6 (pg/mL)	<7	80.2			
ESR (mm/h)	2—13	66		12	2
Ferritin (μg/L)	15.0—200.0	7996			

ESR-erythrocyte sedimentation rate; BUN — blood urea nitrogen; CRP — C-reactive protein; PCT — procalcitonin; IL-6 — ilnterleukin 6; ALT - alanine aminotransferase; AST -aspartate aminotransferase; INR -international normalized ratio; CK - creatine kinase; LDH - lactate dehydrogenase; NT-proBNP - N-terminal prohormone of brain natriuretic peptide; GGT - gamma-glutamyl transferase, AP - alkaline phosphatase; PT - prothrombin time.

TTE performed 48 h after the initiation of the treatment showed improvement of the left ventricle function, LVEF 40—45%. Angiotensin-converting-enzyme inhibitors and beta-blockers were introduced. Microbiological cultures (blood cultures, urine culture, sputum) were negative and therefore the antibiotic treatment was terminated. The patient received the hepatitis B vaccine in childhood. CMV IgG, EBV VCA/EA IgG, EBV EBNA IgG antibodies were detected in the serum. Anti HCV was negative.

A multidisciplinary team including intensivists, infectious disease specialists, and cardiologists jointly treated the patient.

Laboratory tests on the seventh hospital day indicated improvement of myocardial and liver function and a decrease of the inflammatory markers (Table 1). The patient was afebrile, hemodynamically stable, and was discharged from the hospital. Medication at discharge included ASA, ramipril, bisoprolol, pantoprazole, and methylprednisolone tablets. An initial follow-up performed 7 days after the hospital discharge indicated complete normalization of inflammatory and cardiac biomarkers and still elevated liver function tests. LVEF was 60%. The final follow-up was performed 30 days after hospital discharge (Table 1).

We described a case of MIS-A that developed approximately one month after an uncomplicated COVID-19 infection. The most pronounced symptoms at the admission were cardiac dysfunction and acute liver injury. A degree of liver and cardiac dysfunction and ethnicity differentiate our patient from previously described cases of MIS-A.

The patient had acute liver injury marked by a thirtyfold increase of ALT, tenfold increase of AST, and a moderate decrease of prothrombin time (PT). During the hospital stay the PT normalized, the concentration of both ALT and AST decreased but remained elevated even at the first

follow-up. Such a degree of liver injury was not yet associated with MIS-A. On the other hand, acute liver injury presenting with elevated AST or ALT was described during the COVID- 19 [5,6]. The origin of liver injury during COVID-19 remains unresolved and could be related to systemic inflammation, SARS-CoV-2 infection (SARS-CoV-2 might directly bind to ACE2-expressing cholangiocytes [7]), or drug administration. Previous research found that systemic release of pro-inflammatory cytokines seems to cause a progression of disease in COVID-19 [6,8], including liver injury as well. Effenberger et al. found an interesting correlation between AST level at the hospital admission and markers of systemic inflammation, including IL-6, CRP, ferritin, and LDH concentration [9]. It is possible that liver injury in our patient could be at least partially explained by cytokine release syndrome or dysregulation of the immune response.

Another interesting feature is significantly and globally reduced ventricular function that rapidly improved which might be at least partially explained by furosemide application and resolution of volume overload. Further improvement of cardiac function is probably due to immune modifying therapy. As to our knowledge only two other cases with severely compromised cardiac function were described, LVEF < 30%. One of those patients was initially treated with ECMO following LVAD and RVAD [6,10]. Recovery in those two patients took longer than in our patient.

Another difference between the described patient and previously reported patients is ethnicity. The presented patient is Caucasian, while the majority of previously reported were of African or Hispanic origin [4].

This report adds to the literature on MIS-A presenting the young patient with no comorbidities, living in a good social environment who presented with severe cardiac and liver dysfunction. The improvement of cardiac dysfunction was prompt and complete, while the resolution of liver injury was slower. The successful treatment of the patient could be considered a result of joint work of experts gathered in multidisciplinary team.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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