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CASE REPORT

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Histopathological findings of pericarditis in a patient with multisystem inflammatory syndrome in children associated with COVID-19: A case report

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Abstract

Multisystem inflammatory syndrome in children (MIS-C), which is associated with the novel coronavirus disease 2019 (COVID-19), has been described as an inflammatory complication of exposure to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It carries a risk of serious and lethal complications, including cardiogenic shock. Here, we report the pathological findings of the pericardium in a 10-year-old child with MIS-C, who developed pericarditis-induced cardiac tamponade. In the patient's pericardium, the numbers of infiltrating $CD68^+$ macrophages; $CD3^+$, $CD4^+$, and $CD8^+$ T cells; and myeloperoxidase$^+$ granulocytes were increased, although the number of $CD20^+$ B cells was not. These findings provide a clue to understanding the pathophysiology of MIS-C.

KEYWORDS

cardiac tamponade, MIS-C, pericarditis, SARS-CoV-2

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C), which is associated with the novel coronavirus disease 2019 (COVID-19), has been described as an inflammatory complication of exposure to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). MIS-C is characterized by persistent fever, abdominal pain, vomiting, diarrhea, skin rash, mucocutaneous lesions and, in severe cases, with hypotension and cardiogenic shock. Centers for Disease Prevention and Control (CDC) criteria for the diagnosis of MIS-C are as follows:[1] age <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological) and no alternative plausible diagnoses and positive for current or recent SARS-CoV-2

Abbreviations: COVID-19, the novel coronavirus disease 2019; CRP, C-reactive protein; CXCL9, C-X-C motif chemokine ligand 9; ESR, Elasticca-Picrosirius red; LVEF, a left ventricular ejection fraction; MIS-C, Multisystem inflammatory syndrome in children; MPO, myeloperoxidase; PLT, platelet count; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

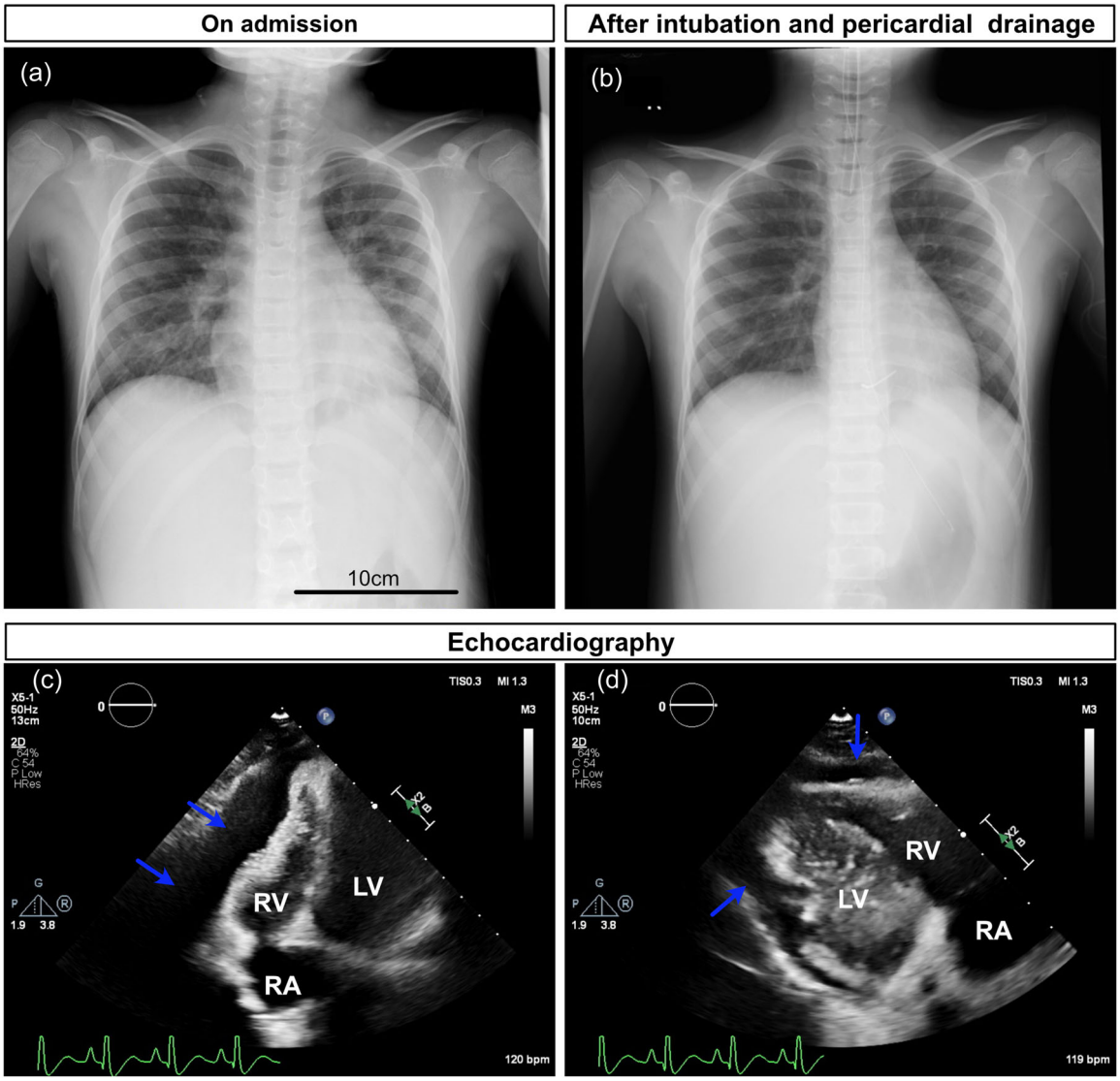

FIGURE 1 The patient exhibited pericardial effusion. (a, b) Chest x-rays; Images obtained on the day of admission (a) or after pericardial drainage (b) are shown. (c, d) Echocardiography showed pericardial effusion (blue arrows).

infection; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms. The World Health Organization (WHO) criteria are described as follows:[2] Children and adolescents 0–19 years of age with fever ≥3 days, and two of the following: (1) Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet). (2) Hypotension or shock. (3) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities. (4) Evidence of coagulopathy. (5) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain). Elevated markers of inflammation. No other obvious microbial cause of inflammation, including COVID-19. In this case, almost all the criteria was fulfilled.

METHOD

Ethics approval and consent to participate

The patient's parents provided written informed consent to the research study approved by the Aichi Children's Health and Medical Centre Ethics Committee. This study is also approved by the Mie University Ethics Committee.

Consent for publication

The parents gave their informed consents for their child's personal or clinical details along with any identifying images to be published in this study.

CLINICAL SUMMARY

We report the case of a previously healthy 10-year-old Japanese girl with MIS-C related to the novel coronavirus disease 2019 (COVID-19), who subsequently developed cardiac failure due to the accumulation of pericardial effusion.

A 10-year-old Japanese girl presented to a nearby hospital with a fever of over 38.5°C, a headache, abdominal pain, and watery diarrhea, which had persisted for 4 days, 1 month after having COVID-19. Laboratory tests revealed mild thrombocytopenia: a platelet count (PLT) of 115 000/μL, an elevated C-reactive protein (CRP) level of 15.8 mg/dL, and a negative result in a COVID-19 antigen test. The attending physician suspected bacterial enteritis and recommended hospitalization, but it was refused. The next day, the patient revisited the hospital, as her condition had not improved. Laboratory tests revealed a PLT of 75 000/μL and a CRP level of 14.5 mg/dL. The patient's blood pressure was 91/47 mmHg. Concomitantly, she presented with bilateral conjunctival hyperemia. The doctor suspected MIS-C, and the patient was transferred to our pediatric intensive care unit for further treatment. After she was admitted to our hospital and treatment was started, her fever subsided and did not return. An echocardiographic examination performed on the day of hospitalization revealed a left ventricular ejection fraction (LVEF) of 53% and mild pericardial effusion without coronary artery dilation. A chest x-ray showed decreased permeability in the lung fields, indicating pulmonary edema (Figure 1a). Laboratory tests showed high concentrations of systemic inflammation markers, including CRP, interleukin-6, C-X-C motif chemokine ligand 9 (CXCL9), tumor necrosis factor-receptor II, ferritin, and D-dimer and an elevated type-B natriuretic peptide level (Table 1). As all of the World Health Organization criteria for MIS-C had been fulfilled, treatment with 2 g/kg/day of intravenous immunoglobulins, 5 mg/kg/day of aspirin, and 2 mg/kg/day of prednisolone was started. That night, after infusions of adrenaline (0.04 μg/kg/min) and milrinone (0.3 μg/kg/min) had been initiated, ventilator management was required because of cardiogenic shock with tachycardia, tachypnea, peripheral circulatory failure, metabolic acidosis and reduced LVEF of 33%. After intubation, infusions of carperitide (0.06 μg/kg/min) and nitroprusside (0.93 μg/kg/min) were also started. The next day, the amount of pleural effusion had increased further (Figure 1c, d); therefore, pericardiectomy and pericardial drainage were performed, and a tissue sample was obtained from the parietal pericardium (Figure 1b and Pathological Findings section). Elevated total protein and lactate dehydrogenase concentrations with increased inflammatory cells in pericardial effusion suggested exudative leakage (Table 1). SARS-CoV-2 RNA was not detected in the pericardial

TABLE 1 Laboratory findings

	Admission	Normal range
Total protein, g/dL	5.56	6.70–8.30
Albumin, g/dL	2.82	3.90–4.90
Albumin/Globulin	1.03	
Urea nitrogen, mg/dL	8.6	8.0–20.0
Creatinine, mg/dL	0.5	0.20–0.80
Uric acid, mg/dL	4.7	2.0–6.0
Ammonia, μg/dL	42	12–66
Glucose, mg/dL	121	70–110
Sodium, mEq/L	132	135–147
Potassium, mEq/L	2.9	3.5–5.0
Chloride, mEq/L	101	98–110
Calcium, mEq/L	8.2	8.5–10.5
inorganic phosphorus, mg/dL	2.2	2.5–4.5
Magnesium, mg/dL	1.8	1.8–2.4
Aspartate aminotransferase, U/L	30	8–38
Alanine aminotransferase, U/L	36	4–44
Lactate Dehydrogenase, U/L	268	106–211
γ-Glutamyl Transpeptidase, U/L	22	16–60
Creatine Kinase, U/L	28	43–165
CK-BB, %	2	0–2
CK-MB, %	2	0–6
CK-MM, %	95	87–98
Amylase, U/L	44	37–125
Total cholesterol, mg/dL	116	130–220
Type-B natriuretic peptide, pg/mL	701	<18.40
Total bilirubin, mg/dL	0.3	0.2–1.2
Direct bilirubin, mg/dL	0.1	0.0–0.2
Indirect bilirubin, mg/dL	0.2	0.1–0.8
White blood cell count,/μL	3330	3500–9100
Lymphocytes, %	12.9	19.0–59.0
Neutrophils, %	82.9	27.0–85.0
Monocytes, %	2.4	0.0–12.0
Eosinophils, %	1.8	<3.0
Basophils, %	0	<3.0
Red blood cells, $x10^4$/μL	389	380–480
Hemoglobin, g/dL	10.7	11.3–15.2
Hematocrit, %	31.3	34.0–43.0
Platelet, $x10^4$/μL	6.5	13.0–36.9
Prothrombin time test, s	14	10.0–13.0

(Continues)

TABLE 1 (Continued)

	Admission	Normal range
Prothrombin time test (international normalized ratio)	1.21	0.85–1.15
activated partial thromboplastin time, s	35.7	
Fibrinogen, mg/dL	375	160–350
D-dimer, μg/mL	2.1	<1.0
Fibrin-fibrinogen degradation products, μg/mL	5.9	<5.0
Antithrombin-III,%	86	75–125
C-reactive protein, mg/dL	14.18	<0.30
H-FABP, ng/mL	2	<6.2
Myosin Light Chain 1, ng/mL	0.1	0.0–2.5
Hi sensitivity troponin T, ng/mL	0.067	0.00–0.014
Ferritin, ng/mL	561.3	3.0–120.0
Procalcitonin, ng/mL	0.89	0.02–0.50
Interleukin-6, pg/mL	51	<3
Interleukin-18, pg/mL	534	<500
CXCL9	6595	<31–83
sTNF-RII	18286	<829–2262
Arterial blood gas analysis		
pH	7.392	7.40 ± 0.05
pCO2, Torr	30.5	36–44
pO2, Torr	295.5	75–100
HCO3-, mEq/L	18.1	22–26
BE, mEq/L	−5.7	−2.2–+1.2
Lactate, mmol/L	4.41	0.5–1.6
Height, cm	136	
Body weight, kg	36	

Pericardial effusion	36 h after admission
Appearance	Yellow cloudy
Specific gravity	1.033
Total protein, g/dL	4.7
Lactate dehydrogenase, U/L	244
pH	7.7
Red blood cells,/μL	$<1 \times 10^4$
White blood cells,/μL	1266
Monocytes,/μL	142
Multinucleated,/μL	1124
Eosinophil,/μL	4
Nucleated cells,/μL	1276

tissue either by the real-time reverse transcription polymerase chain reaction (RT-PCR) or immunohistochemistry against the SARS-CoV-2 nucleocapsid protein.

The patient showed clinical signs of improvement after the treatment. Her inflammatory marker levels and pericardial effusion decreased, and her respiratory status improved. She was extubated and discharged from hospital after 2 weeks and followed up as an outpatient. A control echocardiogram was done and showed no abnormal findings.

The project was approved by Mie University and Aichi Children's Health and Medical Centre ethics committee and this is reported in the manuscript. For human subjects, the investigation was conducted in accordance with the Declaration of Helsinki of 1975. A statement to this effect is included in the manuscript.

PATHOLOGICAL FINDINGS

The excised pericardium showed moderate inflammatory cell infiltration and pericardial fibrosis confirmed by Elastica-Picrosirius red (ESR) staining. No fibrin deposition was observed. These pathological features indicated the characteristic of chronic pericarditis (Figure 2 and Supporting Information: Figure 1). The inflammatory cells were composed of $CD68^+$ macrophages; $CD3^+$, 4^+, and 8^+ lymphocytes; and myeloperoxidase $(MPO)^+$ granulocytes (mainly neutrophils with lobulated nuclei) (Figure 2 and Supporting Information: Figure 1).

DISCUSSION

The novel SARS-CoV-2 pandemic has involved a wide range of clinical manifestations, varying from asymptomatic to SARS.[3] Pediatric COVID-19 patients are believed to exhibit a milder disease course than adults.[4–6] While the complications of COVID-19 in adult patients are more well known, the morbidities experienced by pediatric patients have only recently become apparent.[7] MIS-C is a systemic inflammatory state, which partially overlaps with Kawasaki disease and may rapidly progress to multiorgan failure.[8] It was found that in MIS-C the number of inflammatory cells and inflammatory cytokine production were increased in the peripheral blood;[9] however, few findings from tissue specimens have been reported. There have been a few case reports on the histology of myocarditis in MIS-C patients; however, there have not been any reports about pericarditis in such patients.[10,11] $CD8^+$ T cell infiltration has been predominant in adult COVID-19-associated pericarditis.[12] We observed various inflammatory cell infiltration,

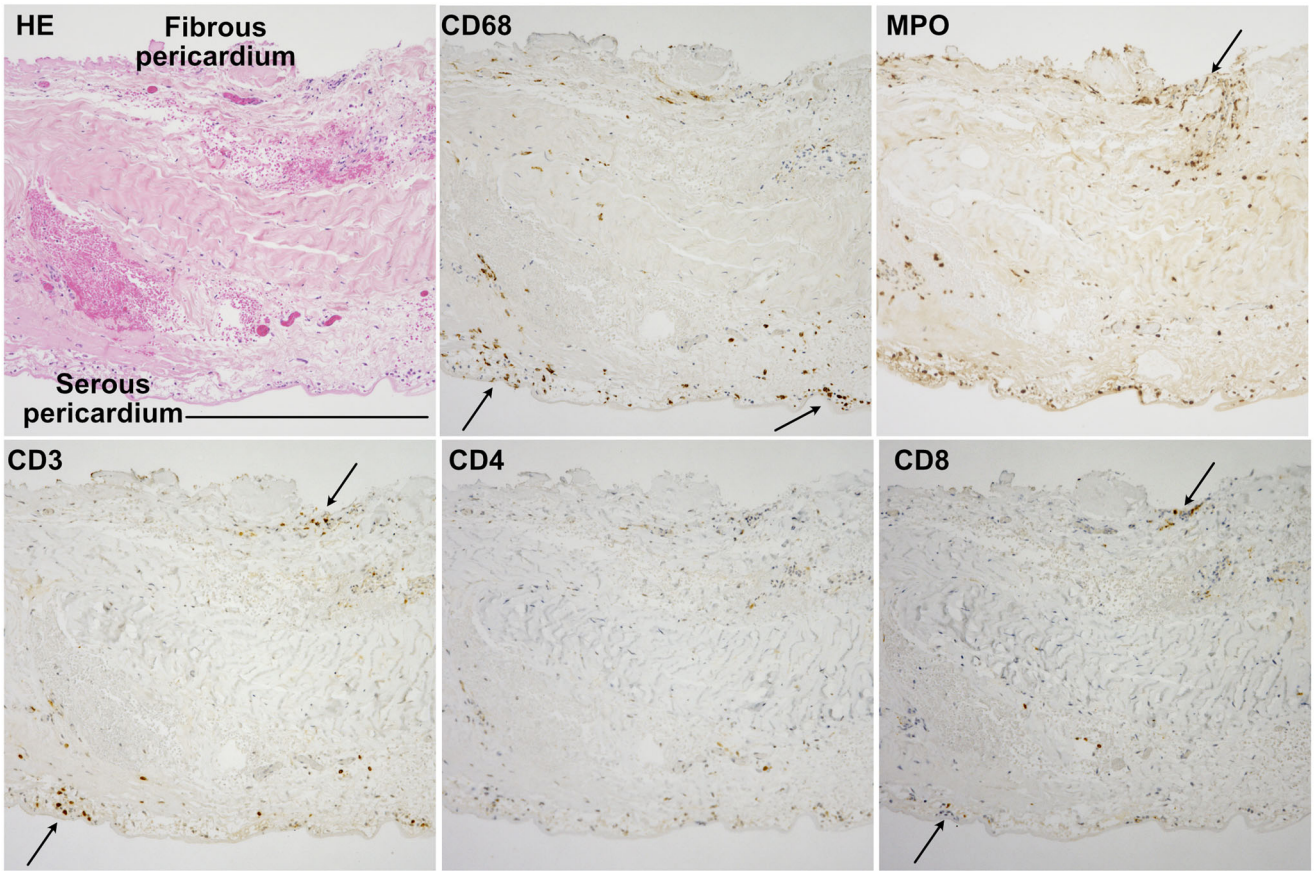

FIGURE 2 Pericarditis with various inflammatory cell infiltration in the multisystem inflammatory syndrome in children patient. Parietal pericardial samples were stained with hematoxylin and eosin (HE). The samples were also subjected to immunostaining as follows: CD68 for macrophages, MPO for granulocytes, CD3 for pan-T cell, CD4 for helper T cells, and CD8 for cytotoxic T cells. The number of CD68 and MPO$^+$ cells was high. In contrast, the number of CD3, CD4, and CD 8$^+$ was low. Scale bar, 100μm.

including CD8$^+$ or CD4$^+$ T cells, macrophages and granulocytes but not CD20$^+$ B cells, in the pericardium of a child with MIS-C, although SARS-CoV-2 could not be detected in the pericardial tissue by RT-PCR or immunostaining. MIS-C associated with SARS-CoV-2 is considered to occur secondary to a cytokine storm that damages numerous organ systems. Our pathological observations support the hypothesis that the indirect effects of SARS-CoV-2 infections on pericardial tissue may have contributed to pericarditis and heart failure in our patient. Hopefully, our findings will help to shed light on the complex inflammatory interactions between SARS-CoV-2 infections, MIS-C, and cardiac dysfunction in children and adolescents with COVID-19.[13]

AUTHOR CONTRIBUTIONS

K.Y. and R.I. were the patient's doctors in charge; K.Y. provided guidance and management for the patient; K.M., K.Y. and K.I-Y. conceived the study and wrote the manuscript with contributions from all of the authors; K.M. was responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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