COVID-19–Related Multisystem Inflammatory Syndrome in Children Presenting With New-Onset Type 1 Diabetes in Severe Ketoacidosis: A Case Series

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OBJECTIVE

To report and describe cases of children presenting with coronavirus disease 2019 (COVID-19)-related multisystem inflammatory syndrome in children (MIS-C) with new-onset type 1 diabetes mellitus (T1DM) in severe diabetic ketoacidosis (DKA).

RESEARCH DESIGN AND METHODS

This prospective observational study was conducted to characterize children with COVID-19–related MIS-C and new-onset T1DM who were in DKA. MIS-C was diagnosed if Centers for Disease Control and Prevention and World Health Organization criteria were fulfilled.

RESULTS

Six cases were identified. The patients were critically ill and in nonfluid responsive shock (combined hypovolemic and cardiogenic or distributive shock). All had cardiac involvement. One patient had a Kawasaki shock-like presentation. All needed aggressive treatment with careful monitoring of fluid balance (because of associated cardiac dysfunction), early institution of vasoactive/inotropic supports, and use of methylprednisolone and intravenous immunoglobulins. The latter are better administered after DKA resolution to avoid undue volume overload and fluid shifts while the patients are in DKA.

CONCLUSIONS

Awareness of MIS-C coexistence with DKA at T1DM onset is crucial for rapid proper management.

The effect of contracting coronavirus disease 2019 (COVID-19) on both development of diabetic ketoacidosis (DKA) in people with type 1 diabetes mellitus (T1DM) (1) and possible delay in diagnosis of new cases until DKA development (2,3) has been documented. More studies on COVID-19 interaction and association with T1DM are underway. COVID-19–related multisystem inflammatory syndrome in children (MIS-C) is a critical illness in which multiple organs show evidence of acute hyperinflammation, leading to shock or multiorgan failure. The condition can be fatal if management is delayed (4,5). To our knowledge, this is the first series of

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children presenting with MIS-C and new-onset T1DM in severe DKA. Their clinical course was more severe. They needed prompt treatment to achieve a favorable outcome.

RESEARCH DESIGN AND METHODS

After diagnosing a critically ill patient with new-onset T1DM in severe DKA who had MIS-C in late May 2020, a prospective study to characterize such cases was conducted between 30 May 2020 and 25 March 2021. MIS-C diagnosis was based on fulfilling Centers for Disease Control and Prevention (CDC) (4) and World Health Organization (5) criteria. These include a child with severe illness with fever $>38^{\circ}$C for $\geq$3 days and involvement of two or more organ systems (such as the following: cardiovascular, gastrointestinal tract [GIT], dermatologic [rash, mucositis, or a Kawasaki-like presentation], hematologic [e.g., in the form of coagulopathy], shock, or hypotension), increase of different inflammatory markers, absence of other microbial causes of inflammation and presence of evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (positive serology or PCR or antigen test or contact with an individual who tested positive within the previous 4 weeks).

DKA diagnosis was based on the International Society for Pediatric and Adolescent Diabetes (ISPAD) definition (6). T1DM diagnosis was made if the patient was not obese, had no signs of insulin resistance, no family history suggestive of monogenic or maturity-onset diabetes of the young, had low C-peptide level, and showed insulin dependency on the usual doses required for a patient with T1DM after resolution of associated inflammation. Autoantibody testing is not routinely performed at our center unless any of the aforementioned criteria are not fulfilled.

Patient clinical data, including vital signs, consciousness level, capillary refill time, urine output (UOP), and complete physical examination findings, were recorded. Laboratory and imaging investigations were performed for each patient (Table 1).

RESULTS

During the study period, 6 of 294 children and adolescents presenting with new-onset diabetes fulfilled the criteria. Of the other 288, 7.7% were not in DKA, and 38.46%, 23.07%, and 30.77% were in mild, moderate, and severe DKA, respectively. Of those with SARS-CoV-2 infection but not MIS-C (n = 26 patients), 50% presented in severe DKA (their condition was much less severe than those with MIS-C).

Data on MIS-C cases are listed in Table 1. Patients with MIS-C included two boys and four girls; their mean age was 10.5 years (range 6–13 years). They were prepubertal children (patient 5 had just started puberty). All were underweight (BMI and BMI percentiles are reported in Table 1), except patient 1. All had low levels of C-peptide ($<$0.1 ng/mL) and no comorbid conditions. None, except patient 5, had a family history of diabetes. All presented in severe DKA (pH 6.7–6.9; serum bicarbonate level 3–5.8 mEq/L), with marked polyuria (range 10–24 mL/kg/h) and marked hyperglycemia (range 630–820 mg/dL).

All patients were critically ill and needed admission to the intensive care unit (ICU). All were feverish, had signs of shock, and needed vasopressor or inotrope support because their shock was nonfluid responsive (combined hypovolemic and cardiogenic or distributive shock). All had disturbed consciousness. A central line was inserted to monitor central venous pressure and bedside echocardiographic evaluation of inferior vena cava size and collapsibility was done to calculate fluids accurately in the presence of associated cardiac dysfunction.

Table 2 details the management of each case. Initial treatment focused on managing shock, DKA (following ISPAD guidelines) and acute kidney injury (AKI), if present. DKA resolution was slower than in patients with DKA but without COVID-19 or MIS-C, with improvement of the severe acidosis in all cases occurring only after institution of proper inotropic or vasoactive drugs. Moreover, initially we were unaware of the possibility of combined MIS-C and severe DKA, but as investigations' results emerged and with additional case evaluation, MIS-C diagnosis was made, and so treatment started after DKA resolution. However, when intravenous immunoglobulin (IVIG) was administered to the next patient during DKA management, severe pulmonary congestion occurred despite a slow IVIG infusion rate (1 g/kg/day). Therefore, afterward, IVIG and methylprednisolone were administered after DKA resolution and shift to subcutaneous insulin. Fluid balance was carefully monitored by central venous pressure, UOP, and inferior vena cava echocardiographic evaluation while the patients were in DKA. Two patients needed anakinra. Diuretics, when needed for heart failure, were initiated after correction of the severe hyperosmolar dehydration and DKA resolution.

All patients needed higher than the usual insulin doses for age and pubertal stage after shift to subcutaneous insulin, and the doses were increased further after methylprednisolone was started (double to triple the usual doses, reaching 3 units/kg/day in these prepubertal children). As levels of inflammatory markers decreased and methylprednisolone was tapered, insulin doses gradually decreased to the usual doses.

CONCLUSIONS

Six critically ill patients with new-onset T1DM presented in severe DKA and MIS-C. They were in a much more critical state than patients with DKA alone or with acute COVID-19 infection. All patients suffered shock with cardiac dysfunction. AKI occurred in two patients, but all six had marked increase in UOP. Institution of proper vascular or cardiac support drugs was essential for improvement. We found it was better to initiate treatment of MIS-C, using methylprednisolone, IVIG, and/or anakinra (as in patients without diabetes), after DKA resolution. Higher subcutaneous insulin doses were needed.

The main question, as the patients presented, was whether these were cases of severe acute COVID-19 or COVID-19–related MIS-C, especially because the first patient had pulmonary involvement that progressed to adult respiratory distress syndrome (ARDS). Our patients' data fulfilled the CDC and World Health Organization criteria for MIS-C. Moreover, in a recent analysis of data of 1,116 patients from 66 hospitals in the United States (7), of whom 539 had MIS-C and 577 had severe acute COVID-19, researchers concluded that patients with MIS-C were more likely to be 6–12 years old, have associated cardiac

Table 1—Data of the patients who presented with MIS-C and new-onset T1DM in severe DKA

Patient no.: sex; age; BMI (percentile)	Clinical data*	Laboratory test results	MIS-C criteria (fever, organ involvement, high levels of inflammatory markers)
1: Male; 13 years; BMI 17 (25th percentile)	Presentation: Fever (40°C), severe sore throat, wheezy chest with dyspnea, weight loss, fatigue, disturbed consciousness. On admission: GCS 10; tachycardia (165/min); poor tissue perfusion (CRT 7 s); BP† 110/70; Kussmaul's breathing; RR 44/min; bilateral fine lung crepitations and sibilant rhonchi all over the chest; UOP 14–16 mL/kg/h.	ABG: pH 6.7, pCO_2 11 mmHg, HCO_{3^-} 3 mEq/L. BG 750 mg/dL, urinary ketones 5+, HbA_{1c} 12.44% (112 mmol/mol), s-potassium 3.7 mmol/L, corrected sodium 132 mmol/L, magnesium 1.9 mg/dL, phosphorous 3.9 mg/dL, s-creatinine 2.9 mg/dL (increased level resolved after 4 weeks), BUN 34 mg/dL, osmolality 340 mOsm/kg.	**Fever** (40°C). **Carditis** (tachycardia, elevated troponin I [0.182 ng/mL], echocardiography showed mild tricuspid regurgitation, dilated LV [EDD 5.3 cm], circumferential pericardial effusion with maximum posterior diameter measuring 8 mm, RVSP 45 mmHg, EF 60%.) **Respiratory involvement** (ARDS with bilateral moderate pleural effusion). **AKI** (s-creatinine 2.9 mg/dL; it dropped to 0.6 mg/dL in 4 weeks). **Hematologic involvement** (lymphopenia [700 cells/μL], high neutrophil-to-lymphocyte ratio (9.14). **Coagulopathy** (D-dimer 6,400 ng/mL). **High inflammatory markers**: high CRP 115 mg/L, high s-ferritin (1,300 ng/mL), high CK total (1,113 IU/L), high LDH (748 IU/L), low s-albumin (2.8 g/dL). Negative cultures with two **positive SARS-CoV-2 PCR** tests.
2: Female; 10 years; BMI 21 (90th percentile)	Presentation: Fever (39°C), weight loss, fatigue, disturbed consciousness. On admission: GCS 10, persistent tachycardia (177/min); nonfluid responsive shock (CRT 6–7 s; cold hands and feet); BP 100/60; Kussmaul's breathing; RR 40/min; UOP 10–12 mL/kg/h; bilateral scattered lung crepitations.	ABG: pH 6.8, pCO_2 12 mmHg, HCO_{3^-} 3.3 mEq/L. BG 680 mg/dL, u-ketones 3+, HbA_{1c} 12% (108 mmol/mol), s-potassium 4.7 mmol/L, corrected sodium 132 mmol/L, magnesium 2.5 mg/dL, phosphorous 3.7 mg/dL. S-creatinine 1.1 mg/dL, BUN 24 mg/dL, osmolality 326 mOsm/kg.	**Fever** (39°C). **Carditis** (persistent tachycardia, nonfluid responsive shock, elevated troponin I [0.095 ng/mL], echocardiography showed mild tricuspid and mitral regurgitation, with pulmonary hypertension [RVSP 39 mmHg], EF 65%). **Respiratory involvement** (basal crepitations, chest CT: CO-RAD score 5 with bilateral peripheral and central patches of ground glass opacities [mainly basal in distribution]). **Hematologic involvement** (lymphopenia [1,000 cells/μL], high neutrophil-to-lymphocyte ratio [8.1]). **Coagulopathy** (D-dimer 3,030 ng/mL). **High inflammatory marker levels**: CRP (160 mg/L), s-ferritin (980 ng/mL), LDH (612 IU/L); low s-albumin (2.4 g/dL). Negative cultures, **positive SARS-CoV-2 IgM and IgG,** negative PCR.
3: Male; 6 years; BMI 15 (between 25th and 50th percentile)	Presentation: Fever (39.5°C), severe abdominal pain and persistent vomiting for 1 week, severe myalgia and fatigue. On admission: GCS 7, irritable, unequal pupils with sluggish reaction to light. Persistent tachycardia (145/min); in hypotensive nonfluid responsive shock (CRT 8 s, BP 70/40, mottled skin). Kussmaul's breathing; RR 38/min; bilateral basal lung crepitations. Tender abdomen; UOP 8–10 mL/kg/h. In few days, developed nonraised, nonblanching erythematous macular rash on hands and feet (were swollen) with edematous, red, dry lips and red oropharyngeal mucosa. Rash later spread to trunk.	ABG: pH 6.9, pCO_2 15.9 mmHg, HCO_{3^-} 3.1 mEq/L. BG 630 mg/dL, u-ketones 4+, HbA_{1c} 11.1% (98 mmol/mol), s-potassium 3.4 mmol/L, corrected Na+ 133 mmol/L, magnesium 2 mg/dL, phosphorous 3.1 mg/dL, s-creatinine 0.9 mg/dL, BUN 6 mg/dL, osmolality 307 mOsm/kg.	**Fever** (39.5°C). **GIT involvement** (persistent abdominal pain and vomiting with tender abdomen). **Shock** requiring vascular and cardiac supports and **mucocutaneous involvement (Kawasaki-shock like picture). Pulmonary involvement** (basal crepitations, chest CT showed bilateral, predominantly peripheral, basal ground glass nodules occupying posterior and superior segments of both lower lobes with a thin rim of pleural effusion). **Myalgia** (severe pains with CK total 344 IU/L). **Coagulopathy** (INR 2.3, D-dimer 910 ng/mL). **High inflammatory marker levels**: neutrophilia (15,700 cells/μL), CRP (60 mg/L), s-ferritin (580 ng/mL), LDH (560 IU/L); low s-albumin (3.1 g/dL). Negative cultures, **positive SARS-CoV-2 IgM and IgG** but negative PCR.

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Table 1—Continued

Patient no.: sex; age; BMI (percentile)	Clinical data*	Laboratory test results	MIS-C criteria (fever, organ involvement, high levels of inflammatory markers)
4: Female; 13 years; BMI 16 (10th percentile)	Presentation: Fever (39°C), weight loss, shortness of breath, disturbed consciousness. On admission: GCS 11; persistent tachycardia (170/min); in severe cardiogenic shock (tender hepatomegaly, elevated JVP, basal lung crepitations, CRT 7 s, BP 90/55). Kussmaul's breathing, RR 40/min; UOP 10–15 mL/kg/h.	ABG: pH 6.8, pCO_2 9 mmHg, HCO_{3^-} 4.1 mEq/L. BG 760 mg/dL, u-ketones 4+, HbA_{1c} 11% (97 mmol/mol), s-potassium 3.3 mmol/L, corrected sodium 132 mmol/L, magnesium 1.7 mg/dL, phosphorous 1.2 mg/dL, s-creatinine 1.4 mg/dL (remained elevated for 2 weeks), BUN 15 mg/dL, osmolality 321 mOsm/kg.	**Fever** (39°C). **Carditis** (cardiogenic shock, tachycardia, elevated troponin I [0.356 ng/mL] and CK-MB [47 IU/L], echocardiograph showed mitral (grade II/IV) and tricuspid (mild) regurgitation, moderately increased RVSP, dilated LV, EF 47%). **AKI**: high s-creatinine level 1.4 mg/dL, which dropped to 0.6 mg/dL after 2 weeks. **Hematologic involvement**: neutrophilia (12,700 cells/μL), severe lymphopenia (780 cells/μL), high neutrophil-to-lymphocyte ratio (16.28). **Coagulopathy** (D-dimer 1,570 ng/mL). **High inflammatory marker levels**: s-ferritin (750 ng/mL), LDH (757 IU/L), increased CRP (35 mg/L), CK total (429 IU/L). Negative cultures, **positive SARS-CoV-2 IgM and IgG,** negative PCR.
5: Female; 10 years; BMI 17 (between 25th and 50th percentile)	Presentation: Fever (38.5°C), fatigue, marked weight loss, abdominal pain and repeated vomiting for 5 days. On admission: GCS 11; tender abdomen all over (especially upper abdomen); in cardiogenic shock (CRT 7–8 s, BP 80/40); persistent tachycardia (155/min); Kussmaul's breathing, RR 36/min; UOP 22–24 mL/kg/h.	ABG: pH 6.7, pCO_2 16 mmHg, HCO_{3^-} 3.6 mEq/L. BG 820 mg/dL, u-ketones 4+, HbA_{1c} 11.2% (99 mmol/mol), s-potassium 5.2 mmol/L, corrected sodium 133 mmol/L, magnesium 1.6 mg/dL, phosphorous 2 mg/dL, s-creatinine 1.2 mg/dL, BUN 20 mg/dL, osmolality 332 mOsm/kg.	**Fever** (38.5°C). Severe **carditis** (shock and acidosis not improving except after adding milrinone and, later, levosimendan, high troponin I level [0.515 ng/mL], echocardiography showed trivial mitral and mild tricuspid regurgitation with dilated LV and EF 42%). **GIT involvement** (acute pancreatitis, elevated s-amylase level 137 units/L, s-lipase 187 units/L). **Hematologic involvement**: neutrophilia (17,100 cells/μL), high neutrophil-to-lymphocyte ratio (8.3), thrombocytopenia (141,000 cells/μL). **Coagulopathy** (D-dimer 2,000 ng/mL). **High inflammatory marker levels**: CRP 106 mg/L, CK total (853 IU/L), low s-albumin (3.1 g/dL). Negative cultures, negative SARS-CoV-2 serology and PCR, but had a **SARS-CoV-2 PCR-positive contact** in the house.
6: Female; 11 years; BMI 13 (<5th percentile)	Presentation: Fever (40°C), fatigue, weight loss, severe abdominal pain and vomiting for several days. On admission: GCS 9; tender abdomen, hepatomegaly, mild ascites. Persistent tachycardia (150/min); nonfluid responsive shock (CRT 7 s, cold periphery); BP 115/88, Kussmaul's breathing, RR 42/min; UOP 20 mL/kg/h.	ABG: pH 6.9, pCO_2 16 mmHg, HCO_{3^-} 5.8 mEq/L, BG 690 mg/dL, u-ketones 4+, HbA_{1c} 17% (162 mmol/mol), s-potassium 4.5 mmol/L, corrected sodium 132 mmol/L, magnesium 1.4 mg/dL, phosphorous 1.7 mg/dL, s-creatinine 1.1 mg/dL, BUN 32 mg/dL, osmolality 334 mOsm/kg.	**Fever** (40°C). **Shock and carditis** (tachycardia, shock responsive to milrinone, high troponin I [0.192 ng/mL] and CK-MB [45 IU/L] values; echocardiography showed trivial mitral and mild tricuspid regurgitation, dilated LV, EF 50%). **GIT involvement**: hepatomegaly (homogenous echocardiographic pattern on ultrasound), mild ascites, high s-amylase level (271 IU/L). **Hematologic involvement**: lymphopenia (800 cells/μL). **Coagulopathy** (D-dimer 2,100 ng/mL). **High inflammatory marker level**: CRP 226 mg/L; low s-albumin (3 g/dL). Negative cultures, **positive SARS-CoV-2 IgM**, negative IgG and PCR.

ABG, arterial blood gas; ARDS, acute respiratory distress syndrome; BG, blood glucose; BP, blood pressure; BUN, blood urea nitrogen; CK, creatine kinase; CO-RAD, COVID-19 Reporting and Data System; CRT, capillary refill time; CT, computed tomography; EDD, end diastolic dimension; EF, ejection fraction; GCS, Glasgow coma scale; INR, international normalized ratio; JVP, jugular venous pressure; LV, left ventricle; RR, respiratory rate; RVSP, right ventricular systolic pressure; s-, serum; u-, urinary; UOP, urine output. *Hospital normal ranges for laboratory values: CRP ≤6 mg/L; serum ferritin 13–150 ng/mL; lactate dehydrogenase 140–271 IU/L; D-dimer ≤500 ng/mL; CK total ≤171 IU/L; CK-MB ≤24 IU/L; high-sensitivity troponin I <0.02 ng/mL; serum amylase 28–100 units/L; serum lipase 7–39 units/L. †All BP values reported in mmHg.

Table 2—Treatment and follow-up data of the included patients

Patient no.	Use of vascular or cardiac supports	Therapy for DKA-related complications	Pharmacologic management of multisystem inflammation and coagulopathy	Length of ICU stay (days), hospital stay (days)	Follow-up data
1	Noradrenaline, assisted mechanical ventilation	None	First case encountered. IVIG was not administered because of lack of awareness of possible MIS-C coexistence. Methylprednisolone pulse therapy at 20 mg/kg for 3 days with tapering over 1 week, then dexamethasone 6 mg for 10 days to wean off oxygen therapy. Enoxaparin and low-dose aspirin. Bicarbonate for associated AKI.	27, 40	Fever persisted for 1 week. AKI resolved in 4 weeks. Weaned off mechanical ventilation after 10 days and off oxygen therapy after 3 weeks, coinciding with drop in levels of inflammatory markers. Echocardiogram at 1 month: persistence of LV dilatation, pericardial effusion, increased RVSP and valvular regurgitation lesions, but mild improvement in EF (67%). Echocardiogram at 6 weeks: pericardial effusion resolved with further improvement of EF (71%), drop in RVSP (from 45 to 33 mmHg) but persistence of LV dilatation. Echocardiogram at 4 months: return of LV dimensions to normal dimensions.
2	Noradrenaline to improve tissue perfusion	None	Methylprednisolone pulse therapy at 20 mg/kg for 3 days with tapering over 3 weeks (did not receive IVIG because EF was 65%). Enoxaparin and low-dose aspirin.	4, 12	Fever resolved within a few days of starting methylprednisolone. Troponin I level dropped (in 2 weeks) with improvement of inflammatory condition. Echocardiographic findings persisted after 1 month although the degree of mitral and tricuspid regurgitation were milder. At 6 months, normal echocardiogram.
3	Noradrenaline and milrinone to treat shock (noradrenaline alone was not sufficient)	IV mannitol for brain edema, two doses needed to regain full consciousness	Methylprednisolone pulse therapy at 20 mg/kg initiated in hospital, but patient was discharged against medical advice. Patient continued oral prednisolone at home but did not receive IVIG. Low-dose aspirin (no anticoagulation because of a high INR).	4, discharged against medical advice	Fever resolved after a few days of anti-inflammatory therapy at home. Shortness of breath continued at home. Rash started peeling off a few days after going home.
4	Noradrenaline and milrinone for cardiogenic shock; assisted mechanical ventilation	None	Bicarbonate for associated AKI in patient 4 only. Methylprednisolone pulse therapy at 30 mg/kg for 3 days with tapering over 3 weeks. Slow infusion of IVIG on 2 g/kg over 2 days. Anakinra (3 mg/kg/day for 5 days) for patients 5 and 6. Furosemide, captopril, and a short course of digoxin. Enoxaparin and low-dose aspirin.	19, 27	Fever resolved a few days after starting methylprednisolone. Gradual improvement of carditis. Diuretic and digoxin stopped after 2 weeks, with improvement of systolic LV function (EF increased to 61%, 65%, and 70% in patients 4, 5, and 6, respectively). Troponin I levels dropped in 2 weeks with improvement of inflammatory condition. Gradual improvement of LV dilatation, which resolved after 1 month. Valvular regurgitation lesions still persisted after 3 months. Completely normal echocardiogram after 6 months. AKI in patient 4 resolved after 2 weeks. Ascites in patient 6 resolved after 2 weeks with start of regression of hepatomegaly. Liver at normal size after 8 weeks.
5	Milrinone, noradrenaline, and, later, levosimendan	None		11, 16	
6	Milrinone	None		8, 22	

EF, ejection fraction; INR, international normalized ratio; IV, intravenous; IVIG, intravenous immunoglobulin; LV, left ventricle; RVSP, right ventricular systolic pressure.

(or cardiorespiratory) or mucocutaneous involvement, have a higher neutrophil-to-lymphocyte ratio (>5), lower platelet count (<150,000/μL) and higher C-reactive protein (CRP) level (>100 mg/L). Vasoactive drugs were needed in 45% of MIS-C cases compared with 9% of acute severe COVID-19 cases. ARDS occurred in 10.6% of MIS-C cases and 9.9% of severe acute COVID-19 cases. In another study (8), researchers found that MIS-C was more severe, ICU admission was more likely, and the odds of shock development or depressed cardiac function were higher in patients aged 6–12 and 13–20 years than in younger patients.

In comparison, our patients were 6–13 years old, presented in severe shock requiring vasoactive or inotropic supports, and all had associated cardiac involvement with elevated levels of inflammatory markers. Patient 3 had a Kawasaki-shock like presentation with mucocutaneous involvement. Patient 1, whose condition progressed to ARDS, had cardiorespiratory involvement, AKI, coagulopathy (D-dimer 6,400 ng/mL), CRP level >100 mg/L, neutrophil-to-lymphocyte ratio of 9.1, and serum ferritin level of 1,300 ng/mL. Therefore, our patients' data strongly favor a diagnosis of MIS-C. As in the other studies, they had severe MIS-C, as they were 6–13 years old.

In a recent CDC report (9), cases of MIS-C reported across the United States were categorized into three classes: class 1 comprised cases without overlap with acute COVID-19 or Kawasaki disease; class 2, cases with pulmonary involvement, possible progression to ARDS, and a higher rate of COVID-19 PCR positivity; and class 3 comprised cases with mucocutaneous involvement that commonly met the Kawasaki disease criteria. Although less common in class 3, cardiac dysfunction occurred in 21% and myocarditis in 16% of patients with class 3 MIS-C. GIT involvement occurred in 97.5%, 86.4%, and 87.9% of patients in classes 1, 2, and 3, respectively. Accordingly, in our series, patient 1 was in MIS-C class 2, and patients 2, 4, 5, and 6 were in MIS-C class 1, and patient 3 was in class 3 (this patient also needed milrinone for shock improvement, indicating associated cardiac dysfunction). In our series, three patients (3, 5, and 6) had GIT involvement.

Another challenge was that some of the clinical features were possible DKA complications or associations. These include the acidosis, poor tissue perfusion and shock (usually hypovolemic or septic), altered consciousness, and inflammation with leukocytosis. However, although electrolyte disturbances and severe acidosis of DKA can affect the myocardium, myocarditis was not reported as a DKA complication. In addition, although vomiting is a DKA symptom, our patients with GIT involvement experienced severe persistent abdominal pain and vomiting for several days before presentation, and symptoms persisted until therapy initiation and drop in the levels of inflammatory markers. Moreover, disturbed consciousness with irritability can occur in DKA, due to brain edema, and can be a neurologic manifestation in MIS-C (7,10). Therefore, the disturbed consciousness of patient 3 presented a challenge. His unequal pupil size indicated possible third cranial nerve palsy, which is one of the diagnostic criteria of ISPAD (6) for brain edema in DKA, and together with the favorable response to mannitol, they indicated that his altered consciousness was due to brain edema. Therefore, although some components of the patients' presentations may be associated with DKA, it is the multisystem inflammation in each patient that makes MIS-C diagnosis possible.

Because proinflammatory cytokines increase in MIS-C (a hyperimmune response to COVID-19 or cytokine storm) and during hyperglycemic crises or DKA (11), combining these two inflammatory entities results in a much worse and more severe condition.

Unfortunately, patient 1 did not receive IVIG, due to lack of awareness of a diagnosis of combined MIS-C and DKA. He received noradrenaline as a circulatory support, together with assisted mechanical ventilation and, later, methyl prednisolone. Fortunately, he recovered but he had the longest ICU and hospital stay (Table 2) and the slowest improvement of left ventricle dilatation and function (compared with patients 4, 5, and 6, who received IVIG and methylprednisolone).

Interestingly, there appears to be only one report of MIS-C with new-onset type 2 diabetes (12). This was in a pubertal Hispanic child with acanthosis nigricans, negative T1DM autoantibodies, and mild acidosis (pH 7.3) at presentation. Moreover, in a period of approximately 3 months, 64 cases were reported at our hospital (13), and 95 cases were reported across all New York Department of Health hospitals (10). Could there be an ethnic or genetic predisposition to MIS-C development, making it more prevalent among Afro-Caribbeans and Egyptians? Only additional studies could tell.

In conclusion, our study highlights the diagnosis of combined MIS-C and severe DKA at T1DM onset. Awareness of this diagnosis is important because early intervention to manage the nonfluid responsive shock, early institution of IVIG and steroids, and an increase in insulin doses, as needed, are crucial to achieve a good outcome. Immunologic or genetic studies may explore the pathophysiology of or predisposition to this condition. Ours was an observational, prospective study limited by the small number of patients with this so-far uncommon condition. A multicentric study may better explore the interplay of COVID-19–related MIS-C with T1DM.

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Author Contributions. All authors discussed, diagnosed, and managed the cases as a team. H.H.A., E.M.F., and A.A.K. conceptualized the research and designed its methodology. H.H.A. collected and organized the data, wrote the manuscript, and had full access to all the data in the study and the final responsibility to submit for publication. For care of included patients, H.H.A. handled the management of diabetic ketoacidosis and diabetes care; E.M.F. handled the pulmonary care; A.A.K. and M.W.A.N. handled the cardiac care; and S.M.M. and A.R.R. were the treating intensivists. All authors contributed to conducting the literature search and revised and approved the submitted manuscript. H.H.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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