Case Report

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New onset diabetes with diabetic ketoacidosis in a child with multisystem inflammatory syndrome due to COVID-19

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Abstract

Introduction: Multisystem inflammatory syndrome in children (MIS-C) is a unique clinical complication of SARS-CoV-2 infection observed in pediatric patients. COVID-19 is emerging as a potential trigger for the development of diabetes in children. Here, we report a patient presenting with MIS-C and new onset diabetes, and discuss the implication and clinical management of these concomitant conditions.

Case presentation: An eight-year-old female presented with hyperglycemia, ketosis and metabolic acidosis consistent with diabetic ketoacidosis (DKA) in the setting of fever, rash, respiratory distress, hemodynamic instability, reduced systolic function with dilation of the left anterior descending artery, and positive SARS-CoV-2 antibodies suggestive of MIS-C.

Keywords: COVID-19; diabetes; MIS-C.

What is new?

- This is the first case of a pediatric patient who presented with simultaneous new onset diabetes and MIS-C.
- Neurological manifestations of MIS-C may have clinical overlap with signs of cerebral edema in DKA.
- The phenotype of MIS-C may include new onset diabetes.

Background

The impact of SARS-CoV-2 on pancreatic beta cell function is under investigation, though it is known that adults with diabetes suffer higher rates of morbidity and mortality from COVID-19 [1]. Interestingly, it remains unclear whether dysregulated immunity, inflammation or beta cell destruction contributes to this increased disease burden. Although pediatric patients appear to be less impacted by COVID-19, there are reports of unique clinical presentations developing either during the acute infectious phase or as a post-inflammatory response [2]. One such syndrome is multisystem inflammatory syndrome in children (MIS-C), which is a post-inflammatory condition that presents with: prolonged fever, elevated inflammatory markers, current or recent SARS-CoV-2 infection, and involvement of two or more organ systems with no other plausible diagnosis [3]. Furthermore, the association of COVID-19 as a trigger for new onset diabetes requires further study as it appears that diabetes incidence may be increasing in the pediatric population [4]. In this report, we discuss a child who presented with both MIS-C and new onset diabetes mellitus. This case highlights the need for further investigation into the association between COVID-19 and beta cell dysfunction not only in the acute infectious state, but also in the post-inflammatory phase.

Case presentation

An eight-year-old previously healthy Hispanic female with obesity presented with four days of polyuria, nocturia, polydipsia, anorexia, fever, diarrhea, vomiting, lethargy, rash and conjunctivitis. She was in her usual state of health until eight weeks prior to presentation at which time she had four days of cough and rhinorrhea with associated

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anorexia and weight loss. She had a history of travel to Mexico two months prior to presentation. During this period, the entire household exhibited similar symptoms, so the parents were tested for COVID-19 and both had SAR-CoV-2 real time (RT) polymerase chain reaction (PCR) testing completed which was negative. The patient was not tested. There is a strong family history of type 2 diabetes (T2D) in the mother, maternal aunt, and maternal grandmother. All three were diagnosed in adulthood and are controlled on oral monotherapy. There is no family history of type 1 diabetes (T1D) nor autoimmune conditions. Review of systems was pertinent for breast growth four months prior to presentation and negative for hyperpigmentation, altered mental status, and COVID-19 exposure.

On presentation to the emergency room, she was febrile to 39.6 °C and tachycardic to 155 beats per minute. Her blood pressure levels ranged from 83/46–113/72 mmHg, and she was breathing 22 breaths per minute with 97% oxygen saturation on room air. Her weight was 43.4 k,g which is 120th percent of the 95th percentile with a body mass index (BMI) *z*-score of 2.08. On examination she was somnolent, though arousable, alert, and oriented. She had bilateral conjunctival injection with limbic sparing. Her pupils were equally round and reactive to light. Her tongue was swollen and bright red with dry mucous membranes. She had scattered cervical lymphadenopathy and was noted to have stage 1 acanthosis nigricans on her neck and axillae. She had tachycardia with no murmurs and did not have Kussmaul respirations. She had erythematous, pinpoint, macules on the palms of her hands with non-pitting lower extremity edema. She had Tanner Stage 2 breast development and pubic hair.

Initial laboratory evaluation, summarized in Table 1, was notable for hyperglycemia, acidemia, ketonuria, glycosuria, inflammation and abnormal coagulation studies. Electrocardiogram showed sinus tachycardia. Bedside echocardiogram (ECHO) revealed decreased contractility. Computed tomography (CT) scan of the head performed due to somnolence showed no abnormalities nor evidence of cerebral edema. Her initial treatment included: normal saline 40 mL/kg, potassium bolus, antipyretics, aspirin, empiric antibiotics, insulin infusion 0.1 unit/kg/h and normal saline with potassium acetate 30 mEq and potassium phosphate 21 mmoL at 124 mL/h.

Three hours after admission to the pediatric intensive care unit, she developed acute worsening of her neurological status during which she was having hallucinations and was in a state of delirium. During this acute change she had worsening fevers, tachycardia, hypotension and respiratory distress. Due to hemodynamic decompensation, she was placed on epinephrine and vasopressin infusions.

Table 1: Initial laboratory findings.

Test	Result	Range
pH	**7.3**	7.35–7.45
Sodium	**127 mEq/L**	135–145 mEq/L
Potassium	**3.4 mEq/L**	3.6–5.0 mEq/L
Chloride	**92 mEq/L**	98–107 mEq/L
Bicarbonate	**14 mEq/L**	22–30 mEq/L
Blood urea nitrogen	18 mg/dL	4–21 mg/dL
Creatinine	0.6 mg/dL	0.3–0.7 mg/dL
Glucose	**429 mg/dL**	60–115 mg/dL
Urine ketones	**≥160 mg/dL**	Negative
Urine glucose	**500 mg/dL**	Negative
Hemoglobin A1c	**12%**	3.0–6.0%
Insulin level	**16.1 uIU/mL**	<19.6 uIU/mL
C-peptide level	Test not performed	–
White blood cell count	**24.14 K/uL**	4.27–11.40 K/uL
Hemoglobin	**13.5 g/dL**	10.6–13.2 g/dL
Platelet count	168 K/uL	199–367 K/uL
Erythrocyte sedimentation rate	**86 mm/h**	1–10 mm/h
C-reactive protein	**24.1 mg/dL**	0.0–0.9 mg/dL
Ferritin	**715 ng/mL**	10–140 ng/mL
Prothrombin time	**19.7 s**	8.8–12.5 s
Partial thromboplastin time	34 s	25–39 s
Fibrinogen	**816 mg/dL**	150–400 mg/dL
D-dimer	**955 ng/mL FEU**	<570 ng/mL FEU
Troponin I	<0.05 ng/mL	0.0–0.05 ng/mL
Brain natriuretic peptide	**2090 pg/mL**	0–100 pg/mL
Triglycerides	**167 mg/dL**	35–135 mg/dL
Thyroid stimulating hormone	0.78 uIU/mL	0.7–6.4 uIU/mL
Free thyroxine	0.87 ng/dL	0.7–2.1 ng/dL
Glutamic acid decarboxylase 65 antibody	<5 I.U./mL	<5 I.U/mL
Insulin autoantibody	<0.4 U/mL	<0.4 U/mL
Islet antigen 2 antibody	0.00 nMOL/L	<0.02 nMOL/L
SARS-CoV-2 RT-PCR	Not detected	–
SARS-CoV-2 IgG	**9.7**	≤0.7
Respiratory viral panel by PCR	Not detected	–
Blood, urine, and CSF bacterial cultures	No growth	–
CSF encephalitis panel	Not detected	–

RT-PCR, real time-polymerase chain reaction; IgG, immunoglobulin G; CSF, cerebrospinal fluid, Bold values indicate abnormal values.

A dedicated ECHO was performed and revealed mildly reduced systolic function with dilation of the left anterior descending artery. Given respiratory distress, a chest radiograph was obtained which revealed a pleural effusion. The patient was placed on continuous positive airway pressure and a furosemide infusion. Her insulin infusion was titrated to goal blood glucose levels of 100–180 mg/dL. Due to worsening mental status, a repeat head CT scan was obtained which was normal. A lumbar puncture was

performed which revealed culture-negative pleocytosis. Antibiotic coverage was broadened with meningitic dosing. Given concern for MIS-C, she was treated with intravenous immunoglobulin (IVIG) 2 g/kg. Due to continued fevers 48 h after IVIG dose, she was treated with infliximab 10 mg/kg and methylprednisolone 1 mg/kg twice daily for five days.

About 72 h after treatment with infliximab, her clinical course improved from a multiorgan perspective: she was weaned to room air; she had restored cardiac function, hemodynamic stability and normal temperatures. She was advanced to a regular diet on hospital day 5 and achieved adequate glycemic control with multiple daily injections by hospital day 7. She was discharged home on hospital day 10. Her final insulin dose was 1.4 units/kg/day. On one-month follow-up, her HbA1c trended down to 7.8 with 80% of blood sugars within target range. Currently, she requires total daily insulin 1.1 unit/kg/day and full dose metformin. Repeat ECHO two months after hospitalization was normal. Her evaluation and treatment are summarized in Tables 1, 2.

Discussion

To our knowledge, this is the first case report to describe a pediatric patient with new onset diabetes and MIS-C. MIS-C is an evolving condition that appears to have a wide spectrum of presenting symptoms and severity. Previous reports about MIS-C have largely commented on cardiac sequelae of disease [5]. A recent case series out of England reported on 58 patients with MIS-C and demonstrated the variability in phenotype [6]. Interestingly, although these cases are being described worldwide, there have not been reports of these cases presenting with concomitant diabetes onset. The finding of these two conditions occurring simultaneously suggests the possibility that COVID-19 impacts beta cell function mechanistically and potentially leads to hastened beta cell death.

There is limited information about the role of acute inflammation in triggering new onset diabetes. There is a case series of two toddler-age children who developed antibody-negative insulin-dependent diabetes who presented in DKA a few months after diagnosis and treatment of Kawasaki disease [7]. These cases together with the one presented in this report support a relationship between acute inflammation and pancreatic endocrine dysfunction leading to diabetes. For patients with MIS-C and post-inflammatory conditions, we suggest monitoring blood sugars and encourage vigilance of development of ketosis and acidosis.

To date, the type of diabetes our patient has remains unclear. On initial presentation, it was thought that she was more likely to have T1D given her age. However, her family history, pubertal status, BMI, and presence of acanthosis nigricans, in the setting of negative diabetes-related antibodies, support a diagnosis of T2D, though the differential diagnosis also includes an insulin resistance syndrome and maturity onset diabetes of the young. Hyperglycemia and acute diabetes mellitus have been observed in the original SARS coronavirus infection in which the virus binds to angiotensin converting enzyme two receptors in the pancreas leading to islet cell damage and reduced insulin release [8]. Animal studies on other viruses have guided a theory that SARS-CoV antibodies can promote disease via antibody-dependent enhancement, which can facilitate continued viral entry and host

Table 2: Remainder of evaluation and treatment.

Age; weight; BMI	Clinical presentation	Imaging results	Pharmacological treatment
Age: 8 years old. Weight: 43.4 kg. BMI: 98.1 percentile (z-score 2.08).	Four days of polyuria, nocturia, polydipsia, anorexia, weight loss, fever, diarrhea, vomiting, lethargy, rash, conjunctivitis.	CT head: normal. ECHO: moderately decreased LV function (EF 26%), LAD dilation (3.3 mm, z-score +1.8). Chest X-ray: low lung volumes, trace pleural effusions.	Hyperglycemia management: Insulin infusion, subcutaneous lantus and humalog. Fluid management: Normal saline, dextrose, potassium acetate, potassium phosphate, furosemide, albumin. Vasopressors: Epinephrine, vasopressin. MIS-C management: Aspirin 40 mg/kg/day, IVIG 2 g/kg x 1, methylprednisolone 1 mg/kg BID x 5 days + 4-day taper, infliximab 10 mg/kg. Antimicrobials: Ceftriaxone 2 g Q12H, vancomycin 15 mg/kg Q8H, clindamycin 10 mg/kg Q6H.

BMI, body mass index; IVIG, intravenous immunoglobulin; BID, twice a day; Q6/8/12H, every 6/8/12 h; CT, computed tomography; ECHO, echocardiogram; LV, left ventricle; EF, ejection fraction, LAD, left anterior descending artery.

inflammation [9]. It can be postulated that antibodies against SARS-CoV-2 may trigger an inflammatory process that leads to beta cell destruction and onset of diabetes. Such a mechanism could help explain why pancreatitis and new onset diabetes mellitus with DKA have been observed in the setting of acute SARS-CoV-2 infection in adults [10, 11]. Further investigation is required to better understand exactly by what mechanism SARs-CoV-2 leads to aberrant beta cell destruction and to understand whether it is a transient vs. permanent phenomenon.

Learning points

1. New onset diabetes can present in the setting of multi-system inflammatory syndrome in children.
2. Inflammatory syndromes may raise the risk for diabetes development.
3. Glycemic monitoring and control should be considered in MIS-C management.

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