Original Research Article

Multisystem Inflammatory Syndrome in Child After Covid-19

Abstract

MIS-C is a condition among pediatric patients with the coronavirus disease of 2019 (COVID- 19), resulting in inflammation of a variety of organ systems, including the heart, lungs, brain, kidneys, gastrointestinal system, skin, and eyes. Here, we investigated a male child aged 6 years who presented by ~~high~~ high-grade fever (39-40 C) for five days, not responding to oral antipyretic, with swollen hands and feet started 2 days after fever, Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea). In addition, he had a difficulty of breathing, erythematous rash on the back appeared on the third day. The patient was admitted to the pediatric intensive care unit and received IV IG once and corticosteroids 60 mg/kg/d for 3 days. ~~Blood~~ The blood test showed elevated inflammatory markers, increased liver enzymes, hypoalbuminemia, thrombocytopenia, and coagulopathy. Finally, he recovered well after IV IG and corticosteroids and was discharged well on corticosteroids with gradual withdrawal within 1 month.

Keywords: Anti-Phospholipid Syndrome, Fever.

Introduction

Severe acute respiratory syndrome (SARS-CoV-2), known to cause the rapid transmission of coronavirus virus disease 2019 (COVID-19), has resulted in high morbidity and mortality worldwide.1 While the virus affects all age groups, children were thought to fare better during the COVID-19 illness, as this population accounted for only 1% to 5% of those diagnosed withthe illness and rarely developed severe disease[1].

Most children with COVID-19 present with a range of signs and symptoms that are not severe or specific enough toprompt disease testing.3One of the rare, yet potentially life-threatening,

complications of COVID-19 in children is a condition knownas a multisystem inflammatory syndrome in children (MISC).

MIS-C is a condition among pediatric patients with the coronavirus disease of 2019 (COVID-19), resulting in inflammation of a variety of organ systems, includingthe heart, lungs, brain, kidneys, gastrointestinal system, skin, and eyes[2, 3].

The true global incidence of MIS-C is uncertain, but it appears to be rare.The first reported cases occurred in the United Kingdom, followed by reports from Canada, Europe, South Africa, and the United States [4].

Most studies demonstrate a lag of 2–6 weeks betweenCOVID-19 infection and developing MIS-C. Over 70% of MIS-Ccases occur in previously healthy patients, with obesity and asthmabeing the most common underlying medical conditions.While MIS-C and Kawasaki disease (KD) share some overlap in symptoms, the epidemiology of MIS-C differs from that of KD. The median age of confirmed cases in MIS-C is 7–11 years, whereas 80–90% of cases of KD occur in children under the age 5 years of age[5, 6].

Males are more commonly affected in both MIS-C (up to 59%) and KD (up to 60%). The rates of MIS-C vary by race, with studies reporting 25–62% of patients ~~being~~ areBlack, 30–40% ~~being~~ areHispanic,15–25% ~~being~~ areWhite, and up to 28% ~~being~~ areAsian [4,5,7,11,14].By comparison, KD more commonly affects infants and young children ofAsian descent, with an incidence of 30 per 100,000 for those of Asianor Pacific Islander descent compared with the lowest incidence amongCaucasians (12 per 100,000)[7].

The complications of MIS-C can be severe, including cardiogenic shockor distributive shock with poor vasomotor tone. In one systematic reviewof 917 patients, 11 (1.9%) patients died. Most patients with cardiacinvolvement (including depressed ventricular function or arrhythmias)typically recover. However, 20–45% of patients may still have a mildly depressed ejection fraction at the time of hospital discharge[8, 9].

Differentiating MIS-C from other hyperinflammatory diseases, such as Kawasaki disease (KD) and toxicshock syndrome, has been challenging for clinicians. Patients with MIS-C tend to be older than those with KD(mean age 8 to 9 years vs 2 to 3 years, respectively), and present with elevated troponin levels.5 Prominent symptoms of abdominal pain and cardiac dysfunction might help to distinguish the condition from toxic shock syndrome and KD[1].

Here, we presented a case of a child who presented with MIS-C symptoms and was managed by ~~a~~ conservative management.

Case presentation

A male child aged 6 years presented ~~by~~ with~~high~~ high-grade fever (39-40 C) for five days, not responding to oral antipyretic, with swollen hands and feet started 2 days after fever, and Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea). In addition, he had a difficulty of breathing, erythematous rash on the back appeared on the third day.

~~Case~~ **The case was subjected to full laboratory testing** (Complete blood count (CBC) with differential.

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), Ferritin

Liver function tests and kidney function tests, urinalysis, and coagulation tests

~~In~~ On fifth day, the patient developed dyspnea, and the swelling increased in bothhands and feet and started also in the face and eyes, conjunctival injection, crackedlips, and strawberry tongue. The abdomen distended and his ability to walkdecreased.

Initial treatment involves resuscitation with carefulassessment for cardiac versus vasodilatory shock using point-of-care ultrasound.

The patient was admitted to the pediatric intensive care unit and received IV IGonce and corticosteroids 60 mg/kg/d for 3 days.

~~Blood~~ The blood test showed elevatedinflammatory markers, increased liver enzymes, hypoalbuminemia,thrombocytopenia, and coagulopathy.

Table 1: Laboratory findings

Hb	9.5 (g/dl)
WBCs	5(10^3/UL)
Neutrophil counts	66%
Lymphocyte	21%
Basophile	1%
Platelets	210(10^3/UL)
RBCS	5.3(10^6/UL)
MCV	77 (fl)
MCH	25.3 (pg)
MCHC	32.8 (g/dl)
CRP	96 (mg/l)
ESR	45 (mm/hr)
Iron	8.7(ug/dl)
Ferritin	196(ng/ml)
Albumin	2.5(g/dl)
Alkaline phosphates	387(IU/l)
AST	200(IU/l)
ALT	100(IU/l)
Creatinine	0.1(mg/d)
Urea	18 (mg/dL)
Prothrombin	15 (seconds)
INR	1.4
D-dimer	4 (mg/L)

Testing for other pathogens: Testing for other viral and bacterial pathogens includes[10]:

- Blood culture
- Urine culture
- Throat culture
- Stool culture
- Nasopharyngeal aspirate or throat swab for respiratory viral panel
- Epstein-Barr virus serology and PCR
- Cytomegalovirus serology and PCR
- Enterovirus PCR
- Adenovirus PCR.

By echocardiography, children had depressed LV function andabnormal strain patterns.Image studies showed pleural effusion, pericardial effusion, and mild ascites.

Table 2: CDC and WHO case definitions of a multisystem inflammatory syndrome in children

CDC case definition
All 4 criteria must be met:
1. Age <21 years
2. Clinical presentation consistent with MIS-C, including **all** of the following: ▪ **Fever:** • Documented fever >38.0°C (100.4°F) for ≥24 hours ▪ **or** • Report of subjective fever lasting ≥24 hours
▪ Laboratory evidence of inflammation • Including, but not limited to,anyof the following: o Elevated CRP o Elevated ESR o Elevated fibrinogen o Elevated procalcitonin o Elevated D-dimer o Elevated ferritin o Elevated LDH o Elevated IL-6 level o Neutrophilia o Lymphocytopenia o Hypoalbuminemia

- Multisystem involvement
  - **2 or more** organ systems are involved:
    - Cardiovascular (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia)
    - Respiratory (eg, pneumonia, ARDS, pulmonary embolism)
    - Renal (eg, AKI, kidney failure)
    - Neurologic (eg, seizure, stroke, aseptic meningitis)
    - Hematologic (eg, coagulopathy)
    - Gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding)
    - Dermatologic (eg, erythroderma, mucositis, other rashes)

- Severe illness requiring hospitalization

3. No alternative plausible diagnoses

4. Recent or current SARS-CoV-2 infection or exposure

- **Any** of the following:
  - Positive SARS-CoV-2 RT-PCR
  - Positive serology
  - Positive antigen test
  - COVID-19 exposure within the 4 weeks prior to the onset of symptoms

WHO case definition
All 6 criteria must be met:
1. Age 0 to 19 years
2. Fever for ≥3 days
3. Clinical signs of multisystem involvement (**at least 2** of the following): ▪ Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
▪ Hypotension or shock
▪ Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP)
▪ Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)
▪ Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain) 4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin)
5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes
6. Evidence of SARS-CoV-2 infection
▪ **Any**of the following: • Positive SARS-CoV-2 RT-PCR • Positive serology • Positive antigen test • Contact with an individual with COVID-19

CDC: Centers for Disease Control and Prevention; **WHO:** World Health Organization; **MIS-C:** multisystem inflammatory.

This table outlines the CDC's and WHO's case definitions of MIS-C. Patients who meet these criteria and who also fulfill full or partial criteria for Kawasaki disease should be considered to have MIS-C

and should be reported. In addition, MIS-C should be considered in any pediatric death with evidence of SARS-CoV-2 infection.

yndrome in children; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; IL-6: interleukin 6; BNP: brain natriuretic peptide; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RT-PCR: reverse transcription polymerase chain reaction; COVID-19: coronavirus disease 2019; PT: prothrombin time; PTT: partial prothrombin time.

Differentiation between MIS-C and acute COVID-19

The clinical features of MIS-C and severe acute COVID-19 overlap. However, differing patterns of clinical presentation and organ system involvement may help differentiate MIS-C from severe acute COVID-19[7, 11, 12]:

- Most MIS-C cases have occurred in ~~children who were previously healthy~~previously healthy children, whereas most cases of severe acute COVID-19 occur in children with underlying health problems.
- Children with MIS-C may have a history of known or suspected SARS-CoV-2 infection in the weeks preceding the onset of febrile/inflammatory symptoms.
- The pattern of organ system involvement differs[7, 11]:
    - Severe pulmonary involvement (~~ie~~i.e., pneumonia, acute respiratory distress syndrome) is a prominent feature in severe acute COVID-19. While respiratory symptoms are common in patients with MIS-C, they are more often secondary to shock and/or impaired cardiac function.
    - Myocardial dysfunction and shock are more common in MIS-C than in severe acute COVID-19.
    - Gastrointestinal symptoms (particularly abdominal pain) are more common in MIS-C.

- Mucocutaneous findings are common in MIS-C and are rarely seen in severe acute COVID-19.

- Inflammatory markers (CRP, ferritin, and D-dimer) tend to be more elevated in MIS-C compared with severe acute COVID-19. In addition, lymphopenia and thrombocytopenia are more common in MIS-C[7].
- SARS-CoV-2 antibody titers are higher in patients with MIS-C compared with acute COVID-19[13].

Table 3: Differentiating between MIS-C and Kawasaki disease

MIS-C	Kawasaki disease
– More commonly affects older children and adolescents (>7 years) – GI symptoms are very common – Myocardial dysfunction and shockare more common – Inflammatory markers [CRP (12–22times normal values), ferritin (1–3times normal values), D-dimer(10–20 times normal values)] moresignificantly elevated – Absolute lymphocyte count andplatelet counts are low	– More commonly affects youngerchildren and infants (<5 years) – GI symptoms are not common – Myocardial dysfunction andshock are less common – Inflammatory markers (CRP,ferritin, D-dimer) are not veryelevated – Leukocytosis andthrombocytosis are common

MIS-C: Multisystem Inflammatory Syndrome in Children; **GI:** gastrointestinal; **CRP:** C reactive protein.Finally, he recovered well after IV IG and corticosteroids and was discharged well oncorticosteroids with gradual withdrawal within 1 month.

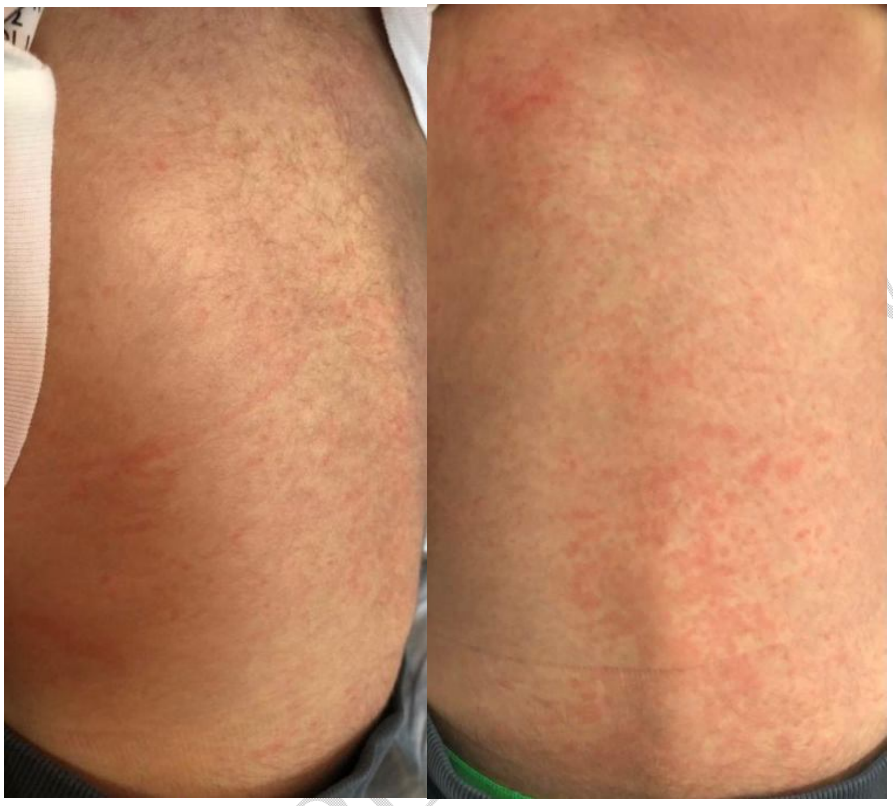

Figure 1 Multisystem Inflammatory Syndrome in Child After Covid-19

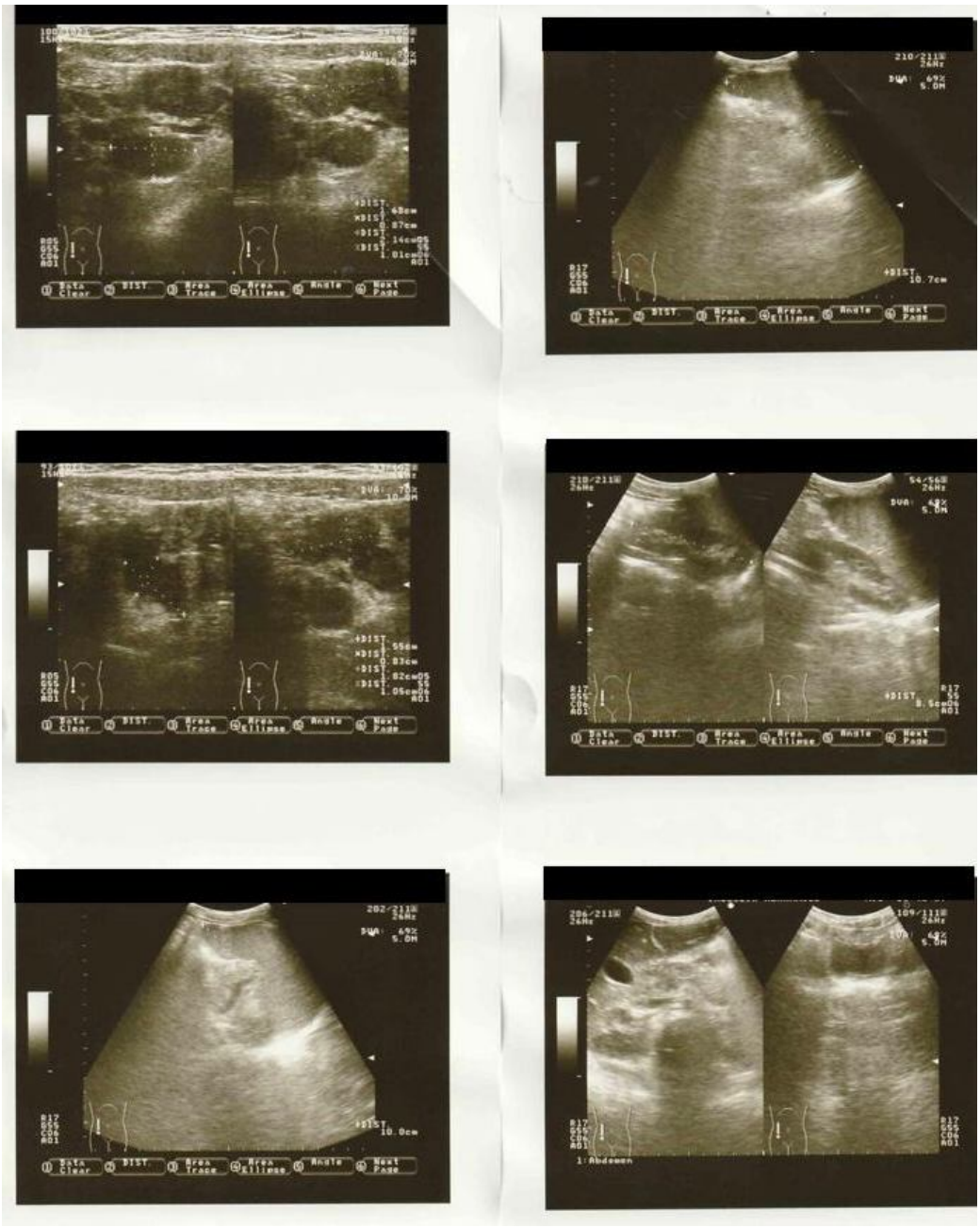

Figure 2:echocardiography images

Discussion

The condition has been termed multisystem inflammatory syndrome in children (MIS-C; also referred to as pediatric multisystem inflammatory syndrome [PMIS], pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 [PIMS-TS], pediatric hyperinflammatory syndrome, or pediatric hyperinflammatory shock).The incidence of MIS-C is uncertain, it appears to be a relatively rare complication of COVID-19 in children, occurring in <1 percent of children with confirmed SARS-CoV-2 infection.

Regarding our study, the case presented by ~~high~~ high-grade fever (39-40 C) for fivedays, not responding to oral antipyretic, with swollen hands and feet started 2 daysafter the fever,and gastrointestinal symptoms (abdominal pain, vomiting, diarrhea). In addition, he had a difficulty of breathing, erythematous rash on the backappeared on the third day.

The presentation of MIS-C varies and can mimic a variety of otherconditions, particularly KD. Table 2 depicts the differences between MIS-Cand KD. Patients with MIS-C may present with gastrointestinal symptoms (abdominal pain, vomiting, or diarrhea are present in 60–100%),neurocognitive symptoms (headache, decreased mental status, or lethargy are present in 29–58%), respiratory symptoms (21–65%), sorethroat (10–16%), and myalgias (8–17%)[11, 14-17].

Severe cases may present with myocardial dysfunction (55%), cardiogenic shock (66%), multisystemic organ failure, and cytokine storm,which can overlap with presentations of KD, septic shock, secondaryhemophagocytic lymphohistiocytosis, and toxic shock syndrome[18, 19].

In one multinational survey of 183 pediatric patients with MIS-C, fever was present in 100% of cases. ~~Shock~~ The shock was present in 43.2% and was more common in older children (mean 9 years vs 7 years). A meta-analysis demonstrated similar results with 100% of patients presenting with fever, followed by 73.3% of patients presenting with diarrhea or abdominal pain, and 68.3% of patients presenting with vomiting. The vast majority of these patients will have a fever for a minimum of 3 days, with a median duration of 4–6 days [17].

Our findings showed that blood tests showed elevatedinflammatory markers, increased liver enzymes, hypoalbuminemia,thrombocytopenia, and coagulopathy[20].

Laboratory markers of inflammation appear to correlate with the severity of illness [9,56]. For example, in one series, children who developed shock had higher CRP values (mean 32.1 versus 17.6 mg/dL), higher neutrophil counts (16 versus 10.8 x 109/L), lower lymphocyte counts (0.7 versus 1.3 x 109/L), and lower serum albumin (2.2 versus 2.7 g/dL) compared with children without shock. In addition, children with shock more commonly had elevated cardiac markers[15].

Cardiac involvement is common in MIS-C. In several large case series, approximately 30 to 40 percent of children had depressed LV function and 8 to 24 percent had CA abnormalities[7].

Children who appear well but in whom MIS-C is a consideration should be tested with CBC, electrolytes, renal and liver function, CRP, and ESR. If CRP ≥ 5 mg/dL or ESR ≥ 40 mm/h ~~are~~ isfound ontesting combined with one of the following other laboratory abnormalities (absolute lymphocyte count < 1.5, platelet count < 150,000, sodium < 135 mmol/L, neutrophilia, or hypoalbuminemia), then fulltesting as described above is recommended. In order to avoid repeat blood draws in this population, it is recommended to obtainextra blood tubes for this additional testing if they are otherwise ~~well~~well-appearing, but MIS-C is suspected[21].

Elevated inflammatory markers are common, with 92% of patientshaving at least 4 of the following abnormalities: elevated ESR(75–80%), elevated D-dimer (67–100%), elevated CRP (90–100%),lymphocytopenia (80–95%), neutrophilia (68–90%), elevated ferritin(55–76%), hypoalbuminemia (48–95%), anemia (70%), thrombocytopenia (31–80%), or increased liver enzymes (62–70%).One large study found that inflammatory markers were higher, andplatelets were lower among those presenting in shock. Cardiovascular involvement is commonly seen, with elevations in BNP/pro-BNP(73–95%) and troponin (50–93%). Acute kidney injury can occur in 8–52%, and laboratory evaluation may also reveal elevated lactate dehydrogenase (10–60%) or hypertriglyceridemia (70%) ifthese laboratory tests are obtained[20, 22, 23].

In a previous study~~which~~that examined 28 children with MIS-C compared with 20 children with classic KD, LV systolic and diastolic function were worse than in classic KD, but CA involvement was less common[24].

Regarding the management of MIS-C The American College of Rheumatology published clinicalguidelines for MIS-C. They included a high level of consensus for administering high-dose intravenous immunoglobulin (IVIG) (2 g/kg based on ideal body weight),glucocorticoids, or both as first-tier agents.21 For patientswith cardiac dysfunction, IVIG may be given as 1 g/kgdaily over 2 days and might require close monitoring anddiuretics.21 Methylprednisolone or other steroids may beused as first-line therapy at 1 to 2 mg/kg daily for patientswho show highly elevated levels of B-type natriureticpeptides, unexplained tachycardia, or ill appearance, butwho have not yet developed shock or organ-threateningconditions.21 If patients do not respond to corticosteroids and IVIG, high-dose corticosteroids (10–30 mg/kg/day) shouldbe considered [21].

Conclusion

MIS-C is a complication of COVID-19 which causes a multi-inflammatory syndrome that can affect nearly any organ system. Common signs and symptoms include fever, gastrointestinal symptoms,neurologic symptoms, and dermatologic findings.

Most patients willhave elevated inflammatory markers and may have an abnormal echocardiogram. Patients will generally requireadmission to an intensive care unit

Treatment includes IVIG, anticoagulation, and considerationof corticosteroids. Aspirin is recommended if there is thrombocytosis.

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