CASE REPORT

Multisystem inflammatory syndrome in a child with low inflammatory markers, persistent hyponatremia, and natriuresis

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Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C) is a rare complication after infection with Coronavirus disease 2019 (COVID-19), and the differential diagnosis from Kawasaki disease is predominantly based on patients' older age and positive anti-SARS-CoV-2 antibodies in most cases.

Case description: We report an "atypical" case of MIS-C in a 3.5-year-old child, with relatively low levels of inflammatory markers, persistent hyponatremia, and hypoalbuminemia, along with exceptionally high levels of brain natriuretic peptide (BNP) and myocardial dysfunction. Persistent hyponatremia was mainly related to natriuresis, while BNP elevation was a marker of the disease severity, reflecting abnormal cardiac function.

Conclusion: Low inflammatory markers in children under the age of five years should not exclude a possible diagnosis of MIS-C. HIPPOKRATIA 2022, 26 (2):83-85.

Keywords: Multisystem inflammatory syndrome, MIS-C, Coronavirus disease 2019, hyponatremia, natriuresis

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Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a rare complication after Coronavirus disease 2019 (COVID-19) infection. According to the Centers for Disease Control and Prevention, diagnostic criteria include age younger than 21 years, fever >38° C, increased inflammatory markers [C-reactive protein (CRP), ferritin, procalcitonin, interleukin 6 (IL-6), fibrinogen], involvement of at least two organ systems (cardiovascular, gastrointestinal, dermatologic, renal, respiratory, hematologic), positive for a current or recent COVID-19 infection or exposure to a suspected/or confirmed case within 4-6 weeks prior to the onset of symptoms, and exclusion of any alternative diagnosis[1].

As some clinical features overlap with Kawasaki disease, differential diagnosis is predominantly based on the higher patient's age (on average 8-11 years) and positive anti-SARS-CoV-2 antibodies in most cases[2-4].

Early diagnosis and treatment of MIS-C are crucial to prevent cardiogenic shock, left ventricular dysfunction, and acute heart failure. High inflammatory markers, along with hyponatremia and hypoalbuminemia, have been associated with the severity of COVID-19 infection and suggest a worse prognosis[5-8].

We report an "atypical" MIS-C case, with mild elevation of inflammatory markers, persistent hyponatremia/hypoalbuminemia, and natriuresis, followed by exceptionally high levels of brain natriuretic peptide (BNP) and myocardial dysfunction.

Case report

A 3.5-year-old boy, unvaccinated for COVID-19, was admitted with a five-day history of high fever, vomiting, and diarrhea. He had experienced a mild COVID-19 infection six weeks before and presented with a low-grade fever for one day, which was confirmed by a serology test. His personal and family history was unremarkable for other underlying diseases. Physical examination showed diffuse erythematous maculopapular rash (Figure 1), palms' edema, conjunctivitis, and cervical lymphadenopathy.

Laboratory tests revealed mild leukocytosis (total leucocyte count 16,600 K/μl, lymphocyte: 9.1 %), anemia (hemoglobin: 10.4 g/dl, normal: 11-14.8 g/dl), and normal platelet count. There was a slight elevation of CRP (3.13 mg/dl, normal <0.5 mg/dl), with elevated levels of procalcitonin (69.54, normal <0.08), ferritin (225 ng/ml, normal <58.7 ng/ml), fibrinogen (497 mg/dl, normal <400 mg/dl), but normal values of IL-6 levels. In addition, sodium and albumin levels were low (125 mmol/l, normal: 138-145 mmol/l, and 2.2 g/dl, normal: 3.8 -5.4 g/dl, respectively), with normal levels of urea and creatinine. Furthermore, BNP and D-dimers were also elevated (209 pg/ml, normal <100, and 3,070 ng/ml, normal <500, respectively). Blood, urine, and stool cultures, nasopharyngeal swab for H1N1, gastrointestinal polymerase chain reaction (PCR) panel, and chest x-ray upon admission did not detect any alternative diagnosis. Serology revealed positive COVID-19 IgM-IgG antibod-

Figure 1: Clinical image of the reported 3.5-year-old child, showing erythematous maculopapular rash on the child's face.

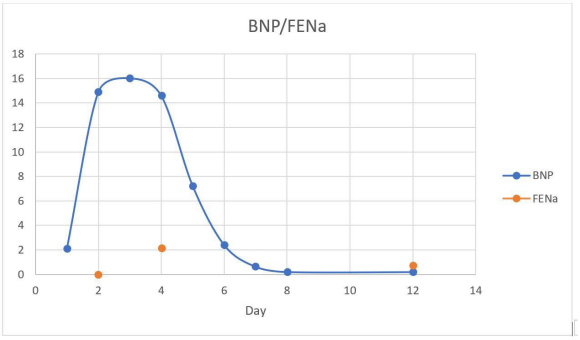

Figure 2: Line graph of brain natriuretic peptide/fractional excretion of sodium levels (BNP/FENa).

ies, while reverse transcription PCR (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was negative.

Although our patient's inflammatory markers were not as high as expected, given the presenting symptoms and the recent COVID-19 infection, there was strong clinical suspicion for MIS-C. Therefore, an echocardiogram was performed, and treatment with intravenous immunoglobulin (2 g/kg), methylprednisolone (2 mg/kg), and low-dose of aspirin was commenced orally. Furthermore, human albumin (2 g/kg) was administered, and the hyponatremia was corrected.

The child's fever and rash subsided, but BNP increased sharply to 1,490 pg/ml the following day and up to 1,680 pg/ml accordingly (Figure 2). HsTroponin-I levels were also slightly elevated (41.25 pg/ml, normal <34.2 pg/ml), reaching the peak on the fourth day of hospitalization (82.45 pg/ml), along with BNP levels.

An echocardiogram revealed dilation of both atria and ventricles, moderately impaired systolic function (ejection fraction: 48 %), mild mitral regurgitation, and small pericardial effusion. Inotropic support with milrinone was added, along with furosemide and high doses of methylprednisolone for three days (30 mg/kg). The patient's cardiac function was improved in 48 hours, and BNP was subsequently reduced to 241 pg/ml, so treatment was continued with methylprednisolone (2 mg/kg), captopril, and furosemide orally.

Furthermore, sodium supplementation was continued, due to persistent hyponatremia, while albumin levels remained low, even after albumin administration. In order to investigate persistent hyponatremia/hypoalbuminemia, a 24-hour urine collection was performed, which showed natriuresis [Fractional Excretion of sodium (FENa): 2.19 %, normal <1 %], with normal urine volume and glomerular filtration rate. Natriuresis subsided after BNP normalization (FENa: 0.72 %) (Figure 2).

On the ninth day of hospitalization, the left ventricular systolic function was normalized (EF: 63 %), with resolution of the pericardial effusion. The child was discharged with gradual tapering of corticosteroids, furosemide, and captopril. Laboratory tests gradually improved and normalized (CRP, fibrinogen, and hemoglobin on the sixth day of hospitalization, procalcitonin, ferritin, BNP, and HsTroponin on the eighth day, while at the same time, D-dimers were slightly elevated: 690 ng/ml and then normalized). In the last follow-up (one year later), the patient was asymptomatic, with normal echocardiographic findings.

Discussion

The presented "atypical" MIS-C case is quite challenging. Although the boy fulfilled the clinical criteria for MIS-C (gastrointestinal, dermatologic, and cardiac involvement), the CRP levels were not significantly elevated in multiple measurements. CRP is considered a sensitive biomarker of COVID-19 infection that assesses the disease severity. However, a recent meta-analysis showed that young children with MIS-C, under the age of five years, may experience a mild elevation of inflammatory markers, as observed in our young patient[9]. Furthermore, in the study of El-Shabrawy et al in a cohort of adult patients, receiver operating characteristic curve analysis revealed that a high CRP/albumin ratio (>11.4) predicted better the disease severity and mortality than CRP levels alone[10]. Our patient's CRP/albumin ratio was 14.22, indicating the disease severity.

Hyponatremia has been reported frequently in children with COVID-19 infection, suggesting a worse prognosis[7,8]. Furthermore, hyponatremia has been associated with acute decompensated heart failure and a greater increase in BNP/pro-BNP levels[11].

In our patient, sodium levels were persistently low. In contrast, BNP levels rose sharply concurrently, reflecting the acute myocardial deterioration and indicating that hyponatremia was mainly related to natriuresis (as evidenced by 24-hour urine collection with elevated FENa). Indeed, BNP is released by the myocardium as a response to volume stretching, providing vasodilation and diuresis[11].

Moreover, in our patient, liver dysfunction could not explain persistent hypoalbuminemia, as transaminase levels were normal, and there were no coagulation disor-

ders. It could be related to increased capillary permeability and escape of albumin to the interstitial space in the context of inflammation[12]. Hypoalbuminemia has already been associated with poor outcomes in severe infectious diseases, including COVID-19 adult patients[13]. The therapeutic efficacy of albumin has been explained by a modulatory effect on inflammation and oxidative stress, along with plasma volume expansion[12].

In conclusion, low inflammatory markers in children under the age of five years should not exclude a possible diagnosis of MIS-C. Furthermore, measurements of sodium levels should be incorporated in all MIS-C patients, as persistent hyponatremia could be related to natriuresis and BNP elevation due to cardiac involvement.

As severe MIS-C patients exhibit hyperinflammation and cytokine storm, further studies are needed in children to elucidate the underlying mechanisms of increased inflammatory markers, which remain unclear.

Conflict of interest

Authors declare no conflict of interest.

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