Diagnosis of Multisystem Inflammatory Syndrome in Children in a Resource-Limited Center

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Abstract

Multisystem inflammatory syndrome in children (MIS-C) has become a serious disease entity following the high prevalence of coronavirus disease 2019 (COVID-19) infection with the involvement of gastrointestinal organs, kidneys, heart, and lungs. When the patient presents with mucocutaneous findings such as conjunctival injection, red lips, neurocognitive symptoms, swollen hands and lymphadenopathy, it is always highly recommended to exclude multisystem inflammatory syndrome.

As it affects multiple organs, it can result in more serious consequences. The manifestations depend largely on the organ involved. Therefore, successful management partly depends on the early diagnosis. Many treatment strategies have been put forth to tackle the disorder so far.

Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a condition where different organs of the body can become inflamed including gastrointestinal organs, kidneys, heart, lungs, eye, brain, and skin. It is connected to the recent coronavirus disease 2019 (COVID-19) infection and usually occurs within two to six weeks from the onset. It is a rare clinical entity where the symptoms depend on the organs involved. It is a delayed and post-infectious complication of COVID-19 [1].

As early identification and treatment are key to complete recovery, it is important to investigate patients thoroughly to make an early diagnosis and initiate the treatment as soon as possible. Although a variety of presentations are observed, gastrointestinal symptoms and fever are very common and recent studies put it as high as 80% amongst the presentations [2].

The other common presentations of MIS-C include rash, conjunctivitis, mucous membrane involvement, sore throat, neurocognitive symptoms, respiratory symptoms, and lymphadenopathy. The common investigation findings include elevated inflammatory markers like C-reactive protein (CRP), D-dimer, erythrocyte sedimentation rate (ESR), and procalcitonin with hypoalbuminemia [1].

The MIS-C mimics the symptoms of various other illnesses such as Kawasaki disease, toxic shock syndrome, and hemophagocytosis lymphohistiocytosis [2].

Case Presentation

We report a case of a 17-year-old South Asian girl who presented with fever with nausea, vomiting, watery diarrhea, and redness in both eyes for four days duration. She vaguely remembered any respiratory symptoms within the last two to six weeks prior to the current illness. She had no urinary symptoms. Neither did she have any headache. She did not have any blood or mucoid admixture in the stool (Figures 1-5).
FIGURE 1: Presentation during the illness.

FIGURE 2: Presentation during the illness: the red lips.
FIGURE 3: Presentation during the illness - conjunctival injection.

FIGURE 4: Redness of both the palms.
On examination, she was febrile and had a bilateral conjunctival injection and maculopapular rash on the bilateral upper and lower limbs. There was no neck stiffness and Kernig’s sign was negative. There was no ankle edema. She was tachycardic with a pulse rate of 165 beats/min, regular and good volume with a blood pressure of 80/52 mmHg. There was no murmur on auscultation. Respiratory examination showed a respiratory rate of 22 breaths/min and SpO2 99% on room air. Lungs were clear on auscultation with normal breath sounds. On abdominal examination, there was no hepatosplenomegaly and the neurology examination was unremarkable. The investigation summary is as follows (Table 1).

| Investigations | Date   |       |       |
|---------------|--------|-------|-------|
|               | 26/08  | 27/08 | 28/08 |
| FBC           |        |       |       |
| WBC (10³/µL)  | 9.42   | 17.5  | 16.6  |
| Neutrophils   | 90%    | 89%   | 91.2% |
| Lymphocytes   | 3%     | 5.8%  | 5.2%  |
| Platelets (10³/µL) | 100 | 138   | 133   |
| Hemoglobin (g/dL) | 12  | 11.1  | 11.1  |
| CRP (mg/L)    | 280    | 289   | 216   |
| ESR (mm/h)    |        |       |       |
| LDH (U/L)     | <234   | 409   |       |
| Serum ferritin (ng/mL) | 800 |       |       |
| Troponin I (ng/mL) <0.12 | 3.27 |       |       |
### TABLE 1: The list of investigations done.

| Test                                    | Value 1 | Value 2 | Value 3 |
|-----------------------------------------|---------|---------|---------|
| D dimer (g/mL)                          | <1      | 8.52    |         |
| Serum sodium (mmol/L)                   | 140     | 141     |         |
| Serum potassium (mmol/L)                | 3.9     | 4       |         |
| Serum calcium (mmol/L)                  | 2.1     |         |         |
| Serum creatinine (µmol/L)               | 88      | 102     | 74      |
| Blood urea (mmol/L)                     | 5.7     | 7.6     | 2.8     |
| Alanine transaminase (U/L)              | 28      | 39      | 36      |
| Aspartate transaminase (U/L)            | 31      | 64      | 43      |
| Alkaline phosphatase (U/L)              | 63      | 62      | 59      |
| Gamma glutamyl transferase (U/L)        | 65      | 64      | 60      |
| Total protein (g/L)                     | 65      | 58      | 71      |
| Serum albumin (g/L)                     | 29      | 29      | 21      |
| Serum globulin (g/L)                    | 36      | 33      | 52      |
| Total bilirubin (µmol/L)                | 11      | 10.7    | 10      |
| INR                                     | 1.82    | 2.23    | 1.2     |
| APTT                                     | 23.3    | 34.8    | 31      |
| Procalcitonin (ng/mL)                   |         |         | 83      |
| Urine full report pus cells and red cells and albumin (/hpf) | 4-6 & 8-10 & Trace |
| Blood culture                           | No growth |         |         |
| Urine culture                           | No growth |         |         |
| Blood picture                           | Likely due to infection |         |         |
| Chest X-ray                             | Normal   |         |         |
| ECG                                     | Sinus tachycardia |         |         |
| 2D echocardiography                     |         |         |         |
| Ultrasound scan abdomen                  | R/S pleural effusion, Peri cholic fluid collection |         |         |

Amongst the clinical manifestations of MIS-C, fever for more than three days, mucocutaneous symptoms like rash, conjunctivitis, red swollen lips, and strawberry tongue along with myalgia were all present. On top of that, the patient had gastrointestinal symptoms in the form of nausea, vomiting, and diarrhea. Neurocognitive symptoms like irritability and headache were also present. 2D-Echocardiography confirmed cardiac involvement with mild global hypokinesia with an ejection fraction of 50%. Rapid antigen test and COVID-19 polymerase chain reaction (PCR) were negative. COVID-19 antibody testing revealed a past infection.

She was started on intravenous immunoglobulin (IVIG) 2 g/kg as an infusion over 12 h. Aspirin 75 mg was also started. After the cultures, broad-spectrum antibiotics such as IV cefotaxime and vancomycin were initiated. Upon admission, subcutaneous enoxaparin sodium 30 mg mane was also added. IVIG was followed by IV methylprednisolone 1 g per day pulse therapy for three days. It was transitioned to oral prednisolone 1 mg/kg regimen which was planned to be tapered off over the period of four weeks. The patient made a complete recovery with the satisfactory improvement of the clinical parameters and significantly reduced
inflammatory markers after five days of initiation of therapy (Figures 6-8).

FIGURE 6: Appearance of the legs after recovery.
FIGURE 7: Appearance of the eyes after recovery.

FIGURE 8: Appearance of the mouth and tongue after recovery.

Discussion

In patients younger than 20 years old, who present with fever for more than three days and marked
gastrointestinal symptoms with evidence of past COVID-19 infection, MIS-C must be considered as a possible differential diagnosis [3]. It must be remembered that this particular syndrome must be considered in children with features of typical and atypical Kawasaki disease and toxic shock syndrome. Other probable differential diagnoses include bacterial sepsis, severe acute COVID-19 infection, systemic lupus erythematosus (SLE), hemophagocytosis lymphohistiocytosis (HLH), and macrophage activation syndrome (MAS) [4]. In our patient, we excluded the most probable differential diagnosis although some of the investigations were not available.

According to the World Health Organization (WHO) case definition criteria, our patient had a fever for more than three days with persistent hypotension, acute gastrointestinal symptoms like diarrhea, coagulopathy (international normalized ratio, INR: 2.25), and features of cardiac dysfunction in the form of mild global hypokinesia. In addition, the biomarkers of inflammation ESR, C-reactive protein (CRP), serum ferritin, D-dimer, creatinine phosphokinase (CPK), and lactate dehydrogenase (LDH) were elevated in the absence of other obvious microbial causes of inflammation (blood culture and urine culture were all negative). And there was evidence of past COVID-19 infection (positive COVID-19 antibody testing) [2].

The main mode of therapy in the disease entity is immunosuppression [5]. Along with IVIG (2 g/kg over 8-12 h), steroids have a key role to play in the treatment of MIS-C. Since the thromboembolic complications are described, enoxaparin is also warranted. Antiplatelet mainly aspirin is continued for four weeks from the outset and sometimes until the coronary arteries become normal. In case of refractory MIS-C where the disease fails to achieve remission, a second dose of IVIG is preferred with pulse doses of IV methylprednisolone (30 mg/kg dose- maximum 1 g daily dose) for three to five days [6]. In our patient, the accomplishment of the recrudescence with the first dose of IVIG was evident so that a second dose was not warranted.

Usage of adjunctive therapies is uncertain. IL-1 inhibitors (IV anakinra 2-10 mg/kg/dose - maximum 100 mg dose), IL-6 inhibitors (tocilizumab 4-8 mg/kg per dose) [7], and convalescent plasma from recovered COVID-19 patients are tried.

The follow-up plan includes monitoring inflammatory markers [erythrocyte sedimentation rate (ESR) and serum ferritin] and echocardiography which is done after one to two weeks in those who have normal function and normal coronary artery dimensions and after two to three days in those with coronary artery dilation until it is stable in size.

In our patient, follow-up 2D echocardiography done in two weeks showed normal cardiac function with an ejection fraction of 60%.

There are several cases of MIS-C reported all around the world. In Moroccan children, there were reported cases of the multisystem inflammatory syndrome as a part of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection [8]. In Sri Lanka, only a few are reported and are successfully treated.

**Conclusions**

In the current COVID-19 prevalent situation, MIS-C must be one of the most important differential diagnoses when a patient presents with mucocutaneous manifestations and multiorgan involvement with any evidence of past COVID-19 infection. Prognosis is excellent following appropriate and early aggressive treatment. Therefore, it is worthwhile to initiate immunosuppressive therapy as early as possible considering the devastating nature of the illness.

**Additional Information**

**Disclosures**

**Human subjects:** Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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