CASE REPORT

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Limping as Presenting Symptom of Multisystem Inflammatory Syndrome in Children (MIS-C): a Case Report of Large Vessel Vasculitis in MIS-C

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ABSTRACT

Background: Multisystem Inflammatory Syndrome of children (MIS) is a pathological condition that occurs in response to a SARS-CoV-2 infection, the syndrome has been described as a "Kawasaki disease"-like illness and the spectrum of associated abnormalities, including vascular complications, remain to be fully defined. **Objective**: The aim of this article was to present a case of MISC presented with limping and associated with large vessel vasculitis. **Case presentation**: In this article we present a case of 10-year-old male presented to emergency department complaining of limping of one-week duration and left hip pain, associated with high grade prolonged fever, abdominal pain and weight loss. The patient was ill looking, couldn't bear weight and was admitted to pediatric intensive care unit. Laboratory workup have rule out infectious and malignant causes as well as known rheumatological causes. Inflammatory markers were elevated. Ultrasound, Doppler ultrasound, CT scan of the affected hip showed evidence of vasculitis extending from the left femoral artery reaching the left common iliac artery with intramural thrombus. According to WHO criteria the patient diagnoses was MIS-C. treatment was started immediately with IVIG and steroids in addition to anticoagulants, dramatic improvement was noticed within 24 hours. Patient was discharged after 10 days of hospitalization. **Conclusion:** MIS-C is a new emerging medical diagnosis after the pandemic of COVID-19. it is described a Kawasaki-like syndrome that affect small to medium vessels. This case reports a large vessel vasculitis associated with MIS-C, it helps the understand the extend of this new syndrome and the variety of complaints that may result from large vessels involvement

Keywords: MIS-C, vasculitis, COVID-19, Thrombosis.

1. BACKGROUND

The COVID-19 pandemic has led to a worldwide health crisis, with a total of 18 million confirmed cases and 690,000 recorded fatalities as of August 5, 2020 (1). It is important to note that, compared to adults, children with acute COVID-19 have a relatively low rate of hospitalization and death (2). In April 2020, the United Kingdom witnessed an increase in cases of a condition referred to as Multisystem Inflammatory Syndrome in Children (MIS-C), leading the Pediatric Intensive Care Society to issue an alert. The condition was later officially named as Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) by the Royal College of Pediatricians and Child Health (3), with an overall incidence rate of 20,375 cases per 100,000 children in the population (4). Multisystem Inflammatory Syndrome (MIS) is a pathological condition that occurs in response to a SARS-CoV-2 infection, the syndrome has been described as a "Kawasaki disease"-like illness and the spectrum of associated abnormalities, including vascular complications, remain to be fully defined. It presents in two forms–one affecting adults and the other affecting children. Both forms of MIS are characterized by febrile syndrome and elevated levels of inflammation, which typically manifest 2 to 6 weeks post-infection (5,6). The development of MIS is attributed to a dysregulated immune response, leading to endothelial dysfunction and a hyperinflammatory state. This in turn leads to capillary leak and multiorgan failure (7).

MIS-Cusually present with fever, GI symptoms including abdominal pain, diarrhea and vomiting, in addition to skin rash, and respiratory symptoms. Only one case has been reported with large vessel vasculitis in association with MIS-C(12), we report the first case of MIS to present with limping secondary to large vessel vasculitis.

2. OBJECTIVE

This case reports a patient with MIS-C syndrome that presented with large vessel vasculitis and deep venous thrombosis. To the best of our knowledge this is the second case of large vessels vasculitis associated with MIS-C

3. CASE PRESENTATION

A 10 years old male presented to the pediatric emergency department at our tertiary hospital, complaining of high-grade Fever and limping. the fever was continuous for 3 weeks prior to presentation, reaching 40.3C, and it was not relieved by acetaminophen, but relieved by NSAIDs. The patient has no respiratory, neurological, hematological or urinary symptoms. No skin changes were noticed. The mother reported abdominal pain and vomiting and unintentional 20 % weight loss over these 3 weeks.

The patient was limping on his left lower limb for one-week duration, with an inability to bear weight. He had left hip pain that started gradually, and progressed to a persistent sharp pain radiating to the thigh, aggravated by movement. Which lead to limitation of his daily activity. The pain was initially controlled with acetaminophen, but later it progressed and became unresponsive to analgesia. The patient denied pain in any other joints, hotness, redness or limb swelling.

The patient has no other comorbidities, and no history of previous surgeries. His family history was insignificant. He was positive for SARS Covid- 19 infection 8 weeks prior to current presentation; it was mild and resolved within few days. He was not vaccinated for Covid-19.

On physical examination, the patient was ill-looking, pale, in pain, unable to walk and unable to bear weight. He was febrile 40 C , tachycardic and tachypnic, normotensive, and O2 saturation 100% on room air. He had no swelling, redness or hotness of all joints, but there was significant tenderness over the left hip with marked decreased range of motion. Abdominal examination revealed mild generalized tenderness with no masses or organomegaly. The rest of the exam was unremarkable.

Laboratory tests revealed high white blood cells (WBC) 18 × 109/L; normal range (4,8 to 10,8 109/L) and high inflammatory markers including D-dimer 2.5 µ/mL (normal range < 0.4 µ/mL), C-reactive protein 67 mg/L (negative <6 mg/L), ESR 120 mm/hr (normal <20 mm/hr) and ferritin 560 ng/mL (normal range 7 to140 ng/mL). Liver enzymes were elevated, kidney function tests and electrolytes were normal. Blood culture and urine culture were negative for any bacterial growth.

Antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) were negative.COVID19 IgG titer was high 2140 IU/mL (Strong positive > 200 IU/mL), and COVID 19 PCR was negative.

Ultrasound (US) of left hip and pelvis revealed a high suspicion of femoral Deep vein thrombosis (DVT). Doppler US showed a massive DVT at the common femoral vein, extending to external iliac vein, proximal part of internal iliac vein and passing to the visualized part of common iliac vein, causing significant venous dilatation and absence of flow, in addition to DVT at superior femoral vein. External iliac artery and common femoral artery showed marked increase in the thickness of intima-media with irregularity, which confirm the diagnosis of vasculitis. However, there was no evidence of hip arthritis

Computed tomography (CT) scan of pelvis and thighs ruled out osteomyelitis and arthritis, and showed concentric mural thickening and wall enhancement of the common iliac, external iliac and common femoral arteries, the findings were consistent with vasculitis. Echocardiogram, electrocardiogram (ECG) and cardiac enzymes were normal. The US of abdomen solid organs was unremarkable.

Thrombophilia workup (including Anti phospholipid, factor 5 leiden mutation (H1299r, Y1702C), MTHFR activity, Protein C, S, antithrombin III and homocysteine) showed no increased risk of thrombosis.

The patient was diagnosed as MIS-c and started on management with two IVIG doses, steroids and aspirin; he received broad-spectrum antibiotics, and low molecular weight heparin (LMWH)

One day one post management the fever subsided, the patient started bearing weight and the limping improved dramatically. Antibiotic were discontinued and the patient was discharged home after six days.

4. DISCUSSION

MIS-C is a new syndrome emerged after the pandemic of COVID-19. It has a variable presentation (Table 1) (9). The majority of cases present to the hospital complaining of persistent fever for four to six days and gastrointestinal symptoms like abdominal pain, vomiting, and diarrhea on the top of the list. Up to two-thirds of the patients may have a rash, conjunctivitis, and mucous membrane involvement. Although severe respiratory involvement is not common, some of the patients may develop respiratory manifestations such as tachypnea and labored breathing (8, 9).

According to world health organization (WHO) the main age group affected by MIS-C is children less than 19 years old (1). For diagnosis to be done. First, Fever must be present for at least three days. Second, there must be evidence of inflammation by the elevation of one of the following: ESR, CRP or Procalcitonin. Third, Evidence of COVID-19 positive by PCR; positive by antigen test; positive by serology; or likely COVID-19 contact should also be present. All these should be associated with at least two of the following clinical symptoms including: Rash, conjunctivitis and mucocutaneous in-

Presenting symptoms	Mean Frequency rate %
Gastrointestinal symptoms	80
Fever	100
Rash	60.5
Conjunctivitis	55.5
Sore throat	13
Respiratory symptoms	43
Neurocognitive Symptoms	43.5
Mucous membrane involvement	51.5
Myalgia	12.5
Lymphadenopathy	11
Swollen hands/feet	12.5

Table 1. The frequency of variable presentations of MIS-C

flammation, hypotension or shock, cardiac involvement, coagulopathy, and acute GI symptoms. Exclusion of any obvious microbial cause should be done to complete the diagnosis of MIS-C.

This patient presented with prolonged fever, limping and elevated inflammatory markers and manifested by gastrointestinal, hematologic and vascular involvement, as well as a positive serology test for recent SARS-CoV-2 infection, meeting the WHO criteria to diagnose MIS-C. The absence of mucocutaneous manifestations and coronary artery abnormalities on echocardiography makes Kawasaki disease a less likely diagnosis. In addition, Kawasaki disease usually affects children at a younger age (14).

MIS-C has been described as a "Kawasaki disease"-like illness affecting small and medium sized vessels. To our knowledge there is one case has been previously reported of large-vessel arteritis in association with MIS-C (19).

Other distinct features of MIS-C manifested in this case include the predominance of gastrointestinal symptoms manifested as severe abdominal pain and persistent vomiting leading to significant weight loss.

Similar to prior reports (15, 16), the elevation of inflammatory markers including prothrombin time, fibrinogen, D-dimer, AST, ferritin, ESR and CRP were pertinent abnormalities in this patient.

Salman et al has reported a MIS-C case manifesting with extensive aortic and branch artery abnormalities including aortitis, mural thrombus, saccular aneurysms and severe stenosis of the left renal artery ostium in a teenager presented with fever, palpitation, fatigability, vomiting and hypertension (12). In Salman et al, the patient had cardiac involvement, the arteritis in aorta and renal artery were diagnosed based on radiological finding and biopsy findings. The reported case was treated with steroids, IVIG and tocilizumab.

In our case There was no cardiac involvement in this case and we depend on radiological findings to diagnose arteritis, no biopsy was needed. CT angiography showed evidence of common iliac, external iliac and common femoral arteritis manifested as concentric mural thickening and wall enhancement. in addition, there were deep venous thrombosis extending from the common femoral vein through the internal iliac vein reaching the common iliac vein, also a DVT involving the external iliac vein and superficial femoral vein. The thrombotic findings are concordant with the hypercoagulable state described in adult patients with SARS-CoV-2 (17, 18).

Thrombophilia screening was against inherited causes of DVT; the dramatic improvement of the clinical status 24 hours after starting steroids and IVIG was in favor of MIS-C diagnosis. Negative viral serology, blood cultures as well as negative ANA and ANCA argue against the infectious and rheumatological causes.

In resistant cases, anakinra, tocilizumab, and infliximab are other therapeutic options that can be used (11). which we didn't need for our patient.

Because MIS-C could be a life-threatening multisystem condition, treatment options are needed urgently. The aim of MIS-C treatment is to suppress systemic inflammation, improve cardiac function, and prevent long-term sequelae (13).

5. CONCLUSION

MIS-C is associated with large vessel vasculitis that is characterized by wall inflammation and associated with thrombosis. Limping could be a presenting complaint of MIS-C. This is the first reported case with limping as a presentation of MIS-C. Early recognition and diagnosis of this rare presentation will raise knowledge about the nature of vascular complications associated with MIS-C.

- **Patient Consent Form**: Written informed consent was obtained from the patient's family.
- **Author's contribution**: All authors were involved in the preparation this article. Final proofreading was made by the first author.
- **Conflicts of interest**: there are no conflicts of interest.
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