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COVID-19 related multi-inflammatory syndrome presenting with uveitis - A case report

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Multi Inflammatory Syndrome (MIS-C) associated with Corona Virus Disease (COVID) in children and young adults presents with a varied clinical spectrum; from that mimicking Kawasaki disease (KD), Incomplete Kawasaki disease to even Hemophagocytic Lymphohistiocytosis. A 14-year-old girl, presented to us, with headache, fever, bilateral uveitis, unilateral cervical lymphadenopathy, oral mucosal changes and abdominal pain. A disproportionate increase in inflammatory markers and Interleukin – 6, in the setting of a negative COVID real-time reverse transcription polymerase chain reaction (RTPCR) and significantly elevated COVID antibody titre confirmed our diagnosis. She was treated with intravenous Immunoglobulin and oral steroids with which she recovered. We want to highlight considering the possibility of MIS-C in children presenting with uveitis at a time when COVID-19 has been conquering the world with community spread.

Key words: COVID-19 in children, multi-inflammatory syndrome related to COVID-19, uveitis

The COVID-19 pandemic has been declared as a public health emergency of international concern.[1] It was thought of as a mild form of disease or asymptomatic infection in children and young adults.[2] But the recently evolved multi-inflammatory syndrome associated with COVID-19 infection (MIS-C) reported in patients less than 21 years is a serious concern in this age group. The World Health Organization (WHO) and the Centre for Disease Control (CDC) have put forward the case definition and management guidelines for the same recently.[3] Here, we report uveitis as the presenting symptom of MIS-C, which is not included in the case definition of MIS-C.

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Case Report

A 14-year-old girl from Medinipur presented to us with complaints of fever, redness and tearing of eyes, and headache for 10 days. She had come in contact with two COVID-19 positive cases (grandfather and uncle living in the same household) 4 weeks prior to the onset of symptoms. She did not have any other significant illness in the past. On examination, she was conscious and oriented, had pallor, right posterior cervical lymphadenopathy (single, 2 × 1 cm size, tender, mobile, discrete) with bilateral nonpurulent conjunctival congestion with no limbal sparing, photophobia, oral mucosal erythema, and strawberry tongue. She was febrile and had tachypnea (38 breaths per min) and tachycardia (124 bpm) and was normotensive. Her weight (56 kg, +1 Z score) and height (158 cm, 0.49 Z score) with a body mass index (BMI) of 22.8 (0.98 Z score) were normal. Her systemic examination was normal. From the history and clinical examination, incomplete Kawasaki disease and MIS-C were considered as provisional diagnoses with possible anterior uveitis – the cause for which was unclear. Laboratory investigations revealed anemia, hypoalbuminemia, and elevated inflammatory markers – erythrocyte sedimentation rate (ESR), C reactive protein (CRP), and Serum Ferritin are shown in Table 1. COVID-19 RT-PCR at admission from the nasopharyngeal swab was negative. Ophthalmological examination revealed normal 6/6 visual acuity and color vision, bilateral nongranulomatous anterior uveitis with the presence of few KPs with Grade 1 cells. There was no flare and vitreous cells/scleritis. There was bilateral papillitis/disc edema. The retinal vessels were normal with no evidence of vasculitis. B-scan was done, and the report was normal. Magnetic resonance imaging (MRI) of the brain with orbit was done, which showed a normal optic nerve sheath diameter (ONSD) and no evidence of demyelination [Fig. 1a and b]. Topical steroids were started in view of anterior uveitis. A possibility of incomplete Kawasaki disease too was considered as the child had fever for more than 5 days with bilateral bulbar conjunctival congestion, oral mucosal erythema with strawberry tongue, unilateral cervical lymphadenopathy, elevated ESR, CRP, anemia, leukocytosis, and hypoalbuminemia.[4] She was given Intravenous Immunoglobulin (IVIg) at a dose of 2 grams per kg and was started on aspirin. An echocardiogram did not show any coronary artery dilatation. After 48 h of IVIg, she continued to have retroorbital pain and developed photophobia as a new symptom in spite of fever subsidence. Her inflammatory markers had shown a rising trend. In view of the pandemic and close contact with COVID-19 patients, COVID-19 antibody

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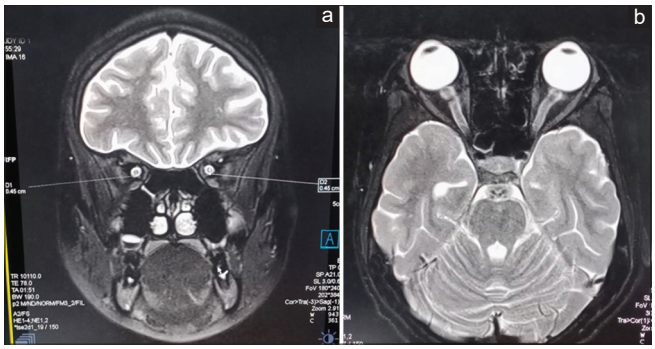

Figure 1: MRI brain with orbit showing normal ONSD (a) and no evidence of demyelination (b)

Table 1: Serial investigation reports of our patient

Investigations	Day 1	Day 3	Day 10
Hemoglobin (gm/dl)	7.6	7.5	7.9
WBC count (cells/mm^3)	16840	8590	7860
WBC (N/L/E/M)	86/10/2/2	82/13/2/3	76/21/2/1
Platelets (cells/mm^3)	300,000	470,000	412,000
ESR (mm/hour)	78	140	38
Ferritin (ng/ml) (Normal -18-160 ng/ml)	633.3	1155.5	470
IL-6 (pg/ml)	9	5500	0.5
D-Dimer (mcg/LFEU)	3.48	17.8	1.77
Se Fibrinogen (mg/dl) (normal -200-400 mg/dl)	376	758	290
CRP (mg/dL)	31.56	389.63	1.87

titer (Anti-SARS CoV 2 Reflex IgG) was done, which was significantly elevated (36.31, Normal <1). Due to the persistence of eye symptoms, elevated inflammatory markers, and high IgG antibody titers for COVID-19, she was given oral steroids at a dose of 2 g/kg/day. Within 48 h of oral steroids, she showed marked improvement in eye symptoms as well as a decrease in the inflammatory marker levels. At discharge, she was well, and oral steroids were continued for 2 weeks, and ocular steroids were gradually tapered and stopped over 1 month. On follow-up at 3 months after discharge, repeat echocardiography was done which was normal, and there was normal vision with no optic disc pallor.

Discussion

MIS-C is a newly defined entity related to COVID-19 infection. With quite variable clinical presentation, the complete clinical and pathological process is still being studied. Usually, it presents within 1 to 6 weeks of exposure to or infection with COVID-19 (1), which was 4 weeks in our case. She had clinical features suggestive of Kawasaki disease like mucosal erythema, unilateral lymphadenopathy, and bilateral conjunctival congestion, although her age was not typical for Kawasaki disease. Uveitis is reported in 66% of children with Kawasaki disease by Burns *et al*.[5] However, our child did not show clinical improvement after IVIg administration, and interestingly her inflammatory markers, which were being monitored, showed further elevation [Fig. 2]. Hence, MIS-C was considered, and she responded well to oral steroids. Another supporting evidence was

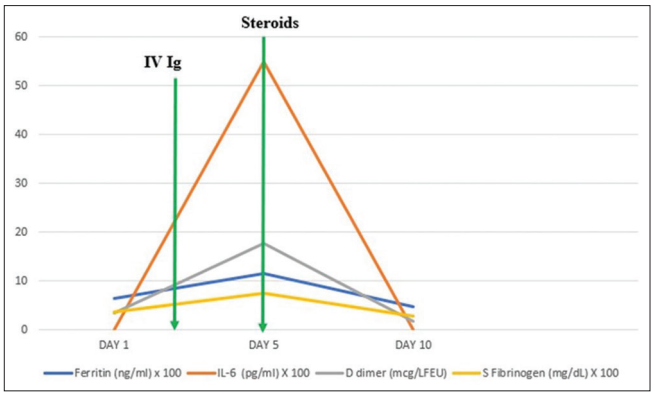

Figure 2: Trend of inflammatory markers and response to treatment

significant neutrophilia (83–85%), which is common in MIS-C and rare in Kawasaki disease.[6] Interleukin 6 levels on Day 3 of admission, even after administration of IVIg worsened to levels of 5500 pg/ml, which has not been reported in MIS-C to date.

In the current scenario, where COVID-19 infection is rapidly spreading, it is essential to have a strong suspicion of MIS-C in children who present with fever, mucus membrane changes, and eye changes. Although conjunctivitis is classically mentioned in the definition, iridocyclitis or uveitis is a symptom that has not been previously reported as a symptom associated with the MIS-C complex in children; however, two reports are there in adults more than 40 years of age.[7,8] The pathophysiology behind the inflammatory process in MIS-C is to be understood completely.[9] Pathogenesis of uveitis caused by inflammatory diseases may be due to molecular mimicry, in which the infectious agent cross-reacts with ocular specific antigens, but the exact mechanism is not completely known.[10] However, both the processes are unregulated immune-mediated inflammatory states which can well explain uveitis also as a presenting symptom in MIS-C. The possible cause of papillitis in our case could be capillaritis or small-vessel vasculitis of the disc vessels.

Management guidelines for MIS-C is IVIg, followed by steroid therapy in those who are unresponsive, followed by biologicals like tocilizumab.[11] Our child required IVIg followed by steroids for complete recovery.

Conclusion

In the present scenario, we intend to convey that in any child or young adolescent presenting with symptoms of uveitis or any other immune-mediated symptoms, the possibility of MIS-C needs to be considered because unknown manifestations are more than known typical manifestations in COVID-19.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Commentary: COVID-19 and ocular inflammation: Where do we stand and where are we headed?

The ongoing coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is an unprecedented health crisis gripping the world. It has infected more than 120 million people and caused more than 2.66 million deaths despite the most aggressive efforts to contain and treat the disease.[1] Epidemiological evidence has undoubtedly shown that the elderly and those with comorbid conditions are at a higher risk of severe COVID-19 and deaths than children.[2] In a systemic review of 45 publications, Ludvigsson has shown that children account for only 1% to 5% of the detected COVID-19 cases, with a milder disease course compared with adults, and deaths being extremely rare.[3] However, although children are usually spared of severe disease and/or death, reports of a multisystem inflammatory syndrome in children (MIS-C) or Kawasaki-like disease secondary to COVID-19 are an emerging cause of concern.[4] Presence of ocular inflammation can also be a part of this altered systemic immune response.[5] In cases with MIS-C, elevated levels of the inflammatory cytokine interleukin-6 have been demonstrated,[6] suggestive of a full-body immune response to the SARS-CoV-2. Such kind of robust immune response is potentially protective for children against disease severity, but at the same time makes them highly vulnerable to inflammatory sequelae such as MIS-C.

Currently, there is an unprecedented effort to control the COVID-19 pandemic. A significant step toward achieving this is the initiation of the COVID-19 vaccination drive on a global scale. Currently, more than 200 vaccine candidates are in various stages of development around the world.[7] The basic platform for vaccine development includes live attenuated virus, recombinant viral-vectored vaccines, inactivated or killed virus, protein subunit vaccines, virus-like particles, and nucleic-based (DNA or mRNA) vaccines.[7] Although the vaccines are developed using various components of the SARS-CoV-2, the primary aim of each one of them is to achieve a long-lasting immune response against the virus. Unfortunately, the durability of the immune response secondary to the vaccine or the natural infections remains unknown. Furthermore, the safety and efficacy of the vaccine in the pediatric population remain unexplored. There are multiple issues in evaluating the COVID-19 vaccine in children, including the medicolegal aspect with the consent, difficulty in assessing the adverse reactions, and the need for a higher number of study participants to reach a level of statistical significance since children are infrequently affected by the disease. Additionally, as COVID-19 poses a life-threatening risk of MIS-C, a similar fatal immune response triggered by the vaccine cannot be completely negated. This can potentially place hitherto normal children at an increased risk of severe adverse immunological reaction after vaccination, which is essentially intended to prevent COVID-19. In fact, MIS-C-like syndrome involving ocular tissue has even been reported in adults older than 40 years of age.[5] Thus, there is a potential risk of ocular inflammation that can be a part of the systemic immune response post-COVID-19 vaccination for all age-groups. Benage and Fraunfelder have reported 289 cases of vaccine-associated uveitis between 1984 and 2014.[8] Among the vaccines, hepatitis B was the commonest cause with a vast majority of affected patients being females (199/289 patients).[8] The median age of the affected patients was 30 years, ranging from 2 months to 86 years.[8]

Based on the current literature related to inflammation associated with COVID-19,[2,3,5] we can postulate that MIS-C and related ocular inflammation can occur more frequently in children than in adults. So it is vital to further explore the pathogenesis and mechanisms related to the deranged immune response and development of MIS-C in COVID-19. With this background, we will be able to effectively evaluate the role and potential risks of COVID-19 vaccines in a pediatric population. At the same time, the vaccination drive is well underway on a global scale in adults and the elderly population. Hence, with