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Case Report

Early Development of Disseminated Intravascular Coagulation in Paediatric Covid-19 Infection

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Abstract

Covid-19 is generally very mild in children but a very small percentage may get severe disease. A severe form of disease occurs 2 - 4 weeks post onset of Covid-19 which has many of the features of Kawasaki's disease has been described and termed multisystem inflammatory syndrome in children. The question that arises is whether we need another syndrome to a Covid-19 complication arising post infection which has many of the clinical features of Kawasaki's disease. The development of DIC early in the onset of Covid-19 infection in children has not been reported before. We report here for the first time a child presenting with Covid-19 infection associated with gastrointestinal bleeding and DIC features. We propose that MIS-C should be renamed Kawasaki's disease induced by Covid-19.

Keywords: *Covid-19; Disseminated Intravascular Coagulation (DIC); Paediatric; Multisystem Inflammatory Syndrome (MIS-C); Kawasaki's Disease; Vasculitis*

Introduction

Since the beginning of the Covid-19 pandemic, over 14 million cases have been reported in the paediatric population accounting for 1 - 2% of Covid-19 cases [1]. Whilst most cases of the disease in children tends to be mild, severe cases may occur rarely with some experiencing a severe exacerbation of the disease occurring 2 to 4 weeks post the infection onset. These late Kawasaki-like manifestations and complications associated with severe systemic hyperinflammatory features, vasculitis and disseminated intravascular coagulation {DIC} has been termed pediatric multisystem inflammatory syndrome associated with COVID-19 or multisystem inflammatory syndrome in children (MISC) [2-8]. MISC has features of vasculitis and might represent post-viral immunological reactions. We have previously reported the association of DIC with severe measles and death in 35 out of 83 children who died of measles and we proposed that a coagulation defect was a complication of severe measles [9]. Common mechanisms may be associated with the development of DIC. Bacterial and/or other viral co-infections may also occur.

The pathophysiology of Covid-19 involves the binding of the virus to the angiotensin converting enzyme 2 (ACE2) expressed by type II pneumocytes in the lungs and other cells such as endothelial cells, pericytes, vascular smooth muscle cells, macrophages, fibroblasts,

T-cells, cardiomyocytes, enterocytes, basal cell epidermal cells, and epithelial tubular distal cells [10,11], followed by cellular entry, dampening the immune response by: induction of double membrane vesicles that lack pattern recognition receptors (PRR) such as toll-like receptors amongst others in which the virus replicates and so its evolutionarily conserved microbial structures called pathogen-associated molecular patterns (PAMPs) that are normally recognized by the PRRs fail to activate the immune response, inhibition of interferon (IFN) responses which dampens innate immunity and promotes free viral replication [12,13,15]. The high and unchecked viral replication in cells induces cytopathic effects which leads to cellular necrosis and apoptotic death. Subsequent to this, increased cellular production of proinflammatory cytokines and chemokines such as TNFα, IL-10, MCP-1, IL-6, IL-1β, MIP-1A and IL-6 occurs in ACE2 expressing cells in lungs and the gut [13,14]. The proinflammatory cytokines from affected local inflammatory sites such as the lungs, spill into the systemic circulation eventually initiating the classic cytokine storm syndrome. This results in a hyperinflammatory {with immune-mediated lung injury} and a hypercoagulable status associated with disseminated intravascular coagulation (DIC) in adults manifesting itself with progressive lung and kidney damage, pulmonary emboli (PE), venous thrombosis, recurrent line obstruction, and strokes. The development of DIC early in the onset of Covid-19 infection in children has not been reported before. We report here for the first time a child presenting with Covid-19 infection associated with gastrointestinal bleeding and DIC features.

Case Report

A 2 year old male patient presented to the referral hospital with cough, diarrhea and vomiting for 3 days. The cough was dry and intermittent. There was no history of TB contact or a family history of asthma. All immunizations were up to date and a Covid-19 antigen test on arrival to hospital was negative. On physical examination, he was pyrexial, temp 38^{o}C, tachycardic, had cervical lymphadenopathy and bilateral crackles on auscultation of the chest but was saturating well with SATs of 98%. The abdomen was distended with shifting dullness and a tympanic percussion note. The heart and neurological examinations were on admission normal. It was thought that he might have a bacterial pneumonia plus acute gastroenteritis and ileus, enteric fever. Because of the lymphadenopathy, pulmonary tuberculosis with lymph node obstruction and abdominal involvement were also considered. Initial investigations showed a C-Reactive Protein of 80 mg/l, normal white cell count, microcytic anemia with a hemoglobin of 10,3 (Mean corpuscular volume 76.2fl) and a normal platelet count of 272 x 10^{9}/L. Blood cultures were negative. The urea and electrolyte panel was normal. Other investigations ordered included a chest x-ray, gastric washings for TB gene Xpert, stool microscopy, culture and sensitivity and a blood culture. He was started on broad spectrum intravenous antibiotics, paracetamol, zinc sulphate and oral rehydration solution. The child remained pyrexial with chills and rigor, started desaturating off oxygen and started having generalized tonic clonic seizures. He now had an abnormal neurological exam with Kernig and Brudzinski signs positive. The chest x-ray showed hilar lymphadenopathy and anti-TB treatment was started with Rifampicin, isoniazid and pyrazinamide and ethambutol.

The patient remained unwell and with an altered mental state. A CT scan of the brain was ordered and it showed maxillary and ethmoidal sinusitis with no brain space occupying lesion, no abnormal leptomeninges or parenchymal or ventricular enhancement, no ventriculomegaly or vasculitic infarcts. After an MDT consultation, it was concluded that this was likely a viral meningitis and anti TB drugs were withheld. The patient had 2 episodes of vomiting coffee ground material and on day 7 post admission. He went into status epilepticus with a worsening neurological examination and a Glasgow coma scale of 8/15. He was admitted to intensive care unit admission and ventilated. The nasogastric tube *in situ* started draining coffee ground material and he was given a stat dose of vitamin K, ranitidine iv, dexamethasone and received an urgent transfusion of fresh frozen plasma. Broad spectrum antibiotics were continued as the patient remained critically ill. A new full blood count showed a thrombocytopenia of 110 x 10^{9}/L, with a hemoglobin of 11.7. Serum D-dimers and FDPs were significantly raised and the WBC = 7.82 x 10^{9}/L. The prothrombin time was 30 seconds (NR 11 - 14) and the activated partial thromboplastin time was 75 seconds (NR 25 - 38) i.e. were all prolonged. A repeat Covid 19 test was done. Covid-19 PCR was positive. Repeat biochemistry showed hyperkalemia, hypernatremia, high urea and transaminitis indicating acute liver injury. The patient developed

severe epistaxis, hematuria, subconjunctival hemorrhage, petechiae on the hard palate and buccal mucosa. The platelet count dropped further to 83 x 10^9/L, WBC 4.89 x 10^9/L, with high urea and the level of consciousness decreased to 3T/15. Despite intensive supportive therapy, he died on day 3 post admission into the intensive care unit.

Discussion

This paediatric Covid-19 case highlights the variable presentations of this disease in children. This child was diagnosed with Covid-19 presenting with disseminated intravascular coagulation and mucocutaneous features presenting at the onset of Covid-19 infection. Apart from the time onset of the DIC and Covid-19, one could say that he had clinical features that fulfilled the WHO criteria for the diagnosis of MISC. the uniqueness of this case is the presentation with DIC very early on in the course of his Covid-19 infection. MISC is a Kawasaki-like complication of Covid-19. The causative agent(s) of Kawasaki are unknown. However, Prof Kussum Nathoo in Harare, Zimbabwe, has observed a number of black children presenting with a viral infections and development of Kawasaki-like complications [unpublished observations]. This patient's Covid-19 antigen tests were negative at presentation to hospital but he was later found to have PCR positive Covid-19 associated with early onset DIC and mucocutaneous lesions. Early detection of DIC and intervention leads to better and improved outcomes in children.

Kawasaki disease (KD) is an acute systemic vasculitis that mainly manifests in children aged < 5 years whose diagnosis usually depends on its clinical manifestations. KD is related to the patient's genetic sensitivity and risk of infection [5]. It has also been termed multisystem inflammatory syndrome in children {MISC}. Although various studies have examined its etiology for more than half a century since its introduction by Tomisaku Kawasaki in 1967, the causative agent has yet to be clarified. Growing body of evidence now points to an infectious trigger. DIC is a complication of severe measles [9]. Measles mimics Kawasaki disease as there are many common features, namely the rash, non-exudative conjunctivitis, straw berry tongue, high temperature and generalised lymphadenopathy. Often children with severe measles die suddenly. Most children with severe measles do not get echocardiography which could detect potential development of coronary aneurysms.

Conclusion

Covid-19 relate Multisystem Inflammatory Syndrome in Children is rare but has poor outcomes. The true global incidence of Covid-91 related MISC is unknown. Multiple diagnostic criteria have been set up to which our patient seemed to fit in. Our case also highlights difficulties of coming up with an exact diagnosis in our African setting where other infectious diseases like tuberculosis continue to top the list with a low threshold for diagnosis and starting treatment. The question that arises now is whether we need another syndrome to a Covid-19 complication arising post infection, which has as we can clearly now see, has many of the clinical features of Kawasaki's disease. There has also been an intense debate on whether MISC in Covid-19 is a new clinical entity or just Kawasaki's disease induced by a viral infection. The emphasis of it being that coining a new disease and syndrome resulted in children not benefitting from the established treatments and management plans in current use for the management of Kawasaki's disease. Our view is that this should now be re-classed as Kawasaki's disease induced by Covid-19 virus. We also propose that Kawasaki's disease may have an infectious trigger (s) which may be viral in nature.

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