Case Report

REACTIVE URTICARIA AND SEVERE THROMBOCYTOSIS IN A CHILD WITH SARS-CoV-2 INFECTION

Lore Van Bruwaene
Robin J Green
Jayneel A Joshi
Jeané Cloete
Department of Paediatrics and Child Health, Steve Biko Academic Hospital, University of Pretoria, South Africa
Email | lorevanbruwaene@gmail.com

ABSTRACT
Coronavirus SARS-CoV-2 has made a significant impact around the world through COVID-19 and its related complications. Individuals with comorbid conditions and the elderly have been at risk of significant inflammatory complications, including the cytokine release syndrome (CRS) and acute respiratory distress syndrome (ARDS). Children, on the other hand, have been less affected and have had less severe disease. However, reports from Europe and North America have described clusters of children and adolescents with paediatric multisystem inflammatory syndrome. Both adults and children have also exhibited a number of unusual disease manifestations. We present the case of a South African child, infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presenting with reactive urticaria and thrombocytosis, further broadening the clinical spectrum of COVID-19 in children.

Keywords: Coronavirus disease 2019, children, urticaria, thrombocytosis

INTRODUCTION

Worldwide, children make up a minority of confirmed cases of coronavirus disease 2019 (COVID-19), usually contributing to between 1% and 5% of total case numbers.[1] Whereas adults typically present with acute respiratory distress syndrome in the second week of illness, the paediatric clinical presentation seems to be milder and atypical, including gastro-intestinal symptoms and fever, with few respiratory symptoms.[2,3] This disparity in clinical presentation between adults and children remains inexplicable. Hypotheses include differences in receptors in the renin-angiotensin system and altered inflammatory responses to pathogens.[4] Recently, reports from Europe and North America have described clusters of children and adolescents requiring admission to intensive care units with a multisystem inflammatory condition with some features similar to those of Kawasaki disease (KD) and toxic shock syndrome (TSS).[5,6] This syndrome seems to be related to COVID-19, based on positive serology in a majority of patients, and is known as paediatric multisystem inflammatory syndrome – temporally associated with SARS CoV-2 (PIMS-TS) in Europe and multisystem inflammatory syndrome in children (MIS-C) in the United States.[5–7] Fortunately, critical illness in paediatric COVID-19 remains rare (~1%), with most cases recovering quickly after treatment; but deaths have been reported.[1] Similarly to data from other countries, the burden of COVID-19 disease in South Africa is lower in young children compared to adults. Children made up 3.3% of COVID-related admissions, despite constituting approximately one-third of the South African population. Of the children aged ≤18 years admitted, 7% were admitted to an intensive care unit, 2% had to be ventilated and 1% died.[8] We present the case of a South African child, infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), who presented with reactive urticaria and thrombocytosis, further broadening the clinical spectrum of COVID-19 in children.

CASE DESCRIPTION

A two-year-old South African girl of African descent, previously healthy and HIV-unexposed, was admitted to a private hospital with a first episode of wheezing. A nasopharyngeal swab sent for polymerase chain reaction (PCR) testing was positive for SARS-CoV-2. Haematological testing was within normal limits. A chest radiograph revealed bronchial wall thickening and left upper-lobe infiltrates (see Figure 1). She was treated with intravenous antibiotics and bronchodilator therapy and never needed oxygen therapy. She was discharged after five days and asked to quarantine at home for 14 days.

The day after her discharge from the private hospital, the child developed a new onset fever, anorexia and an itchy migrating

rash. Given her COVID-positive status, the mother struggled to re-access the private healthcare institution and she was requested to contact our hospital, a tertiary academic centre and a current referral centre for COVID-19 in the region.

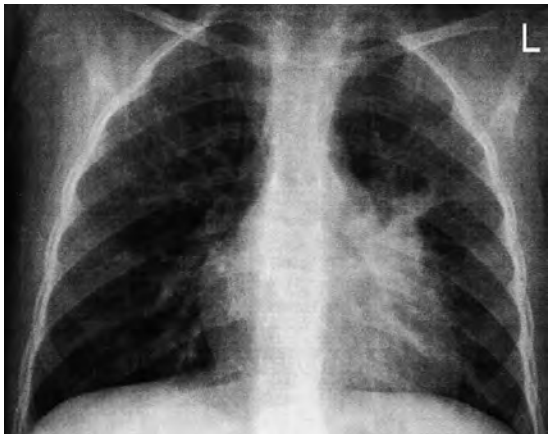

Figure 1: Chest X-ray at COVID-19 diagnosis

On arrival at our hospital, the child appeared generally well and her vital signs were stable, except for a mild tachycardia (152 heartbeats/min). She was pyrexical, with documented fever up to 39.6°C. There was a clear urticarial rash on the trunk and the legs (see Figure 2). The rash was itchy but not painful, and migratory in nature. No respiratory signs were present, neither was there lymphadenopathy nor hepatosplenomegaly, and her mucous membranes and conjunctivae were normal in appearance.

TABLE I: DIAGNOSTIC CRITERIA FOR KAWASAKI DISEASE (KD)[9]

The diagnosis of KD requires the presence of fever lasting at least five days* without any other explanation combined with at least four of the five following criteria:

1. Bilateral bulbar conjunctival injection
2. Oral mucous membrane changes, including injected or fissured lips, injected pharynx or strawberry tongue
3. Peripheral extremity changes, including erythema of palms or soles, oedema of hands or feet (acute phase) and periungual desquamation (convalescent phase)
4. Polymorphous rash
5. Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter)

If ≥4 of the above criteria are present, a diagnosis of KD can be made on day four of illness.

Haematological testing revealed a normal haemoglobin, normal white cell count with mild lymphopenia (3.17×10^9/L), elevated C-reactive protein (CRP) (5.4 mg/dL) and markedly elevated platelets (936×10^9/L). Liver-function tests and albumin were within normal limits. The patient was prescribed antihistamines and was discharged home on the same day.

Given reports on the association between COVID-19 and KD, it was decided to review the child 48 hours later during a short 24-hour admission. During this assessment, the skin rash had disappeared, she was afebrile and clinical examination was completely normal. Repeat haematological testing demonstrated a drop in CRP to 2.1 mg/dL, but persistent thrombocytosis (901×10^3/μL) and new onset anaemia (haemoglobin 9.9 g/dL). Her cardiac sonar was normal. A repeat test for SARS-CoV-2 on nasopharyngeal aspirate was negative. Serology for Epstein–Barr-virus (EBV) and cytomegalovirus (CMV) were negative as well as a multiplex PCR-respiratory virus panel done by obtaining a nasopharyngeal aspirate. No cytokine studies were done. A follow-up date was arranged with the mother for two weeks later.

On follow-up two weeks later, the child was well, her clinical examination was still unremarkable and her blood results had normalised (haemoglobin 11.6 g/dL and platelet count 558×10^3/μL)

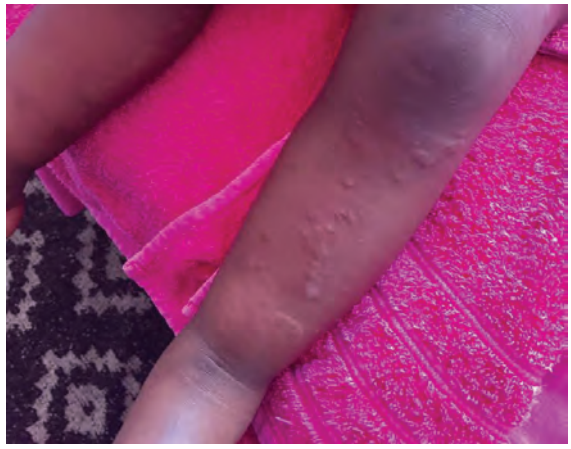

Figure 2: Urticarial rash on the legs one week after COVID-19 diagnosis

DISCUSSION

We present the case of a two-year-old girl who presents in the second week of COVID-19 illness with reactive urticaria and severe reactive thrombocytosis. The patient did not fulfil the diagnostic criteria for KD, since there was no associated mucous membrane or lymph-node involvement (see Table I). The World Health Organization (WHO) case definition for multi-inflammatory syndrome in children was equally not met since there was no multi-system involvement (see Table II). The inflammatory response to SARS-CoV-2 is probably a continuum, with our patient having a milder presentation.

Urticaria wheals are raised, erythematous and usually intensely pruritic. Individual lesions normally last less than 24 hours. They are migratory in nature and do not leave skin changes after resolution. This distinguishes urticaria (alone) from urticarial vasculitis. The most common cause of acute urticaria in children is a viral infection (approximately 60% of children). Dermal mast cells can be activated through the interaction of immunoglobulin (Ig)G and IgE receptor on mast cells. Degranulation of the mast cell results in the release of histamine, serotonin, proteases and tumour necrosis factor alpha. Activated mast cells also release cytokines such as interleukin (IL)-1, with an escalation in human inflammation against the culprit antigen. These pathways lead to the formation of urticaria (wheals).[10]

Urticaria in SARS-CoV-2 infection has been reported in adults, both in Europe and in China,[11] but to our knowledge this is the first paediatric case report. Although the exact pathogenesis of the urticarial reaction is unknown, it is not surprising that SARS-CoV-2 can cause acute urticaria and COVID-19 should from now be considered as a differential in these patients.

TABLE II: WHO CASE DEFINITION FOR MULTI-INFLAMMATORY SYNDROME IN CHILDREN[7]

All 6 criteria must be met:
1. Age 0–19 years
2. Fever for ≥3 days
3. Clinical signs of multisystem involvement (at least two of the following): • rash, bilateral non-purulent conjunctivitis or *mucocutaneous* inflammation signs (oral/hands/feet) • hypotension or *shock* • features of *myocardial dysfunction*, pericarditis, valvulitis or coronary abnormalities • evidence of *coagulopathy* (prolonged PT or PTT; elevated D-dimer) • acute *gastrointestinal* symptoms (diarrhoea, vomiting or abdominal pain)
4. Elevated markers of inflammation (eg ESR, CRP or PCT).
5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal TSS.
6. Evidence of SARS-CoV-2 infection, any of the following: • positive SARS-CoV-2 RT-PCR • positive serology • positive antigen test • contact with an individual with COVID-19

PT: prothrombin time; PTT: partial prothrombin time; ESR: estimated sedimentation rate; CRP: C reactive protein; PCT: procalcitonin; TSS: toxic shock syndrome; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RT-PCR: reverse transcriptase polymerase chain reaction; COVID-19: coronavirus disease 2019.

It should be remembered that children with acute infections often have penicillin prescribed to them by healthcare practitioners. In practice, it is impossible to dissociate between these two distinct causal factors. Urticarial skin reactions can occur if penicillin (eg amoxicillin and ampicillin) is prescribed to children in the presence of a viral infection (eg EBV) and this is often wrongly pursued as a penicillin allergy. It is possible that the virus–drug association also triggers urticaria in COVID-19. Therefore, it seems prudent to withhold antibiotic therapy in mild paediatric COVID-19 infection, unless bacterial superinfection is suspected.

Thrombocytosis was another surprising finding in this case, as most paediatric COVID-19 patients have a normal or decreased platelet count on presentation.[3] Secondary thrombocytosis is typically caused by the over-production of proinflammatory cytokines, especially IL-6. Interestingly, IL-6 is strongly related to the severity of COVID-19 in adults.[4] Unfortunately, IL-6 could not be measured in this patient.

This case report, and more recent reports, indicates that children present with a unique inflammatory response to SARS-CoV-2, not leading to ARDS but presenting as KD, TSS, urticaria and thrombocytosis. Consistent with the adult literature, children from an African background seem to be at higher risk of severe disease from acute COVID-19 infection and are significantly over-represented in case reports of MIS-C.[1] African countries might face many challenges in the care of COVID-19-infected children, including difficulties in clinical follow-up once they are quarantined at home.

In the absence of cytokine measurements, immune pathways acting against the SARS-CoV-2 are merely assumptions and clearly more data and research are needed to better describe the inflammatory response in children infected with this novel virus, possibly trying to explain the skin and haematological manifestations of this disease.

LEARNING POINTS

- Children, as with adults, can experience clinical worsening in the second week of illness caused by SARS-CoV-2, in keeping with the proposed pro-inflammatory pathophysiology.
- Symptoms after discharge for COVID-19 warrant further investigation; in addition, systems need to be in place to receive these children in an appropriate isolation room and to transport them safely to and from home.
- Urticaria and thrombocytosis are inflammatory responses to SARS-CoV-2 and are further broadening the clinical and biochemical characteristics of COVID-19 in children.
- In paediatrics, testing for SARS-CoV-2 should be considered widely in a range of clinical scenarios, including skin rashes.

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DECLARATION OF CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

This article has been peer-reviewed.

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