Severe acute inflammatory myositis and rhabdomyolysis in paediatric SARS-CoV-2-associated MIS-C (multisystem inflammatory syndrome in children)

Faeeza Cassim, Abdullah Jalaluddin Soni, Susan Murphy

SUMMARY
We present the case of a 12-year-old African girl infected with SARS-CoV-2 who was admitted to a tertiary academic hospital in Johannesburg with severe acute inflammatory myositis complicated by rhabdomyolysis and acute kidney injury requiring renal replacement therapy and intensive care. She also fulfilled the diagnostic criteria for multisystem inflammatory syndrome in children.

BACKGROUND
On 31 December 2019, the WHO described a cluster of unidentified pneumonia cases arising in Wuhan City, China. The causative agent isolated, now known as 'Severe Acute Respiratory Syndrome Coronavirus 2 2019 (SARS-CoV-2)', was declared a global pandemic and has now spread to over 200 countries worldwide and has infected over 10 million people to date.

While most severe cases have been reported in adults, the paediatric population appears to present with predominantly mild symptoms and disease course, except in children who have comorbid disease.

Typical symptoms in children include fever, cough, fatigue, dyspnoea, anorexia, diarrhoea and myalgia. Myositis with rhabdomyolysis has been described in adult case reports, as well as in one adolescent. To our knowledge, this is the first such case in a child younger than 16 years and the first to be described in the context of multisystem inflammatory syndrome in children (MIS-C).

CASE PRESENTATION
A 12-year-old African girl with no known comorbidities presented with progressive weakness of the lower limbs with associated myalgia and dyspnoea. She indicated that, a week prior to presentation, she had sore throat and fever and noticed weakness in her lower limbs. There was no history of any positive SARS-CoV-2 contacts. Two days prior to admission, she developed diarrhoea and mild dyspnoea and lost the ability to walk due to worsening weakness in her lower limbs and myalgia. On clinical examination she was noted to be tachypnoeic, with diminished reflexes: 1 out of 4 in the upper limbs and 2 out of 5 in the lower limbs, and the weakness was noted to be worse proximally than distally. She had normal sensation to touch and proprioception, and there was no loss of bladder or bowel function.

INVESTIGATIONS INCLUDING TREATMENT
Initial laboratory investigations revealed raised inflammatory markers: C reactive protein 221 mg/L, erythrocyte sedimentation rate 81 mm/hour, ferritin 1447 μg/L, and leucocytosis (40.8×10⁹/L) with neutrophilia and lymphopaenia. Serum albumin was low (23 g/dL), and both C3 (0.59 g/L) and C4 (0.06 g/L) were also low (table 1). Her admission serum creatine kinase (CK) was 7134 U/L, which subsequently increased to >22 000 U/L. Serum phosphate was elevated, and serum lactate dehydrogenase was markedly elevated (>2500 U/L), as well as aspartate aminotransferase (2227 U/L), with only a moderately elevated alanine aminotransferase (457 U/L). The rest of liver function tests were normal aside from low serum albumin (23 g/dL). She had myoglobinuria on urinalysis and acute kidney injury (urea 39 mmol/L, creatinine 248 μmol/L). These biochemical abnormalities were typical of severe muscle injury and rhabdomyolysis. Renal function did not improve with fluid resuscitation and required renal replacement therapy (RRT) and intensive care unit (ICU) admission on day 2. Acute indications for RRT were hyperkalaemia unresponsive to medical management (potassium 7.5 mmol/L), anuria and ureamic encephalopathy. She required intubation due to the low GCS (7 out of 15), presumed to be a consequence of uremic encephalopathy.

Reverse transcription PCR test for SARS-CoV-2 was positive. Her HIV result was negative, and an autoimmune screen, including antinuclear factor, anti-b2 glycoprotein, anti-sm, Anti nuclear antibody (ANA) and Anti neutrophil cytoplasmic antibody (ANCA), was also negative.

She had normal cerebrospinal fluid result. Blood cultures did not grow any organisms. Radiological investigations included normal chest X-ray, renal
ultrasound and CT of the brain. Her echocardiogram showed a structurally normal heart with an ejection fraction of 65% and no coronary artery dilatation.

Her blood urea and creatinine improved, and the encephalopathy resolved with clearance of blood urea. RRT was stopped on day 5 of her ICU admission and she was able to be extubated on day 2 in the ICU. She complained of muscle pain which improved with administration of non-steroidal anti-inflammatory drugs and continuation of prednisone. Muscle weakness persisted, but improved gradually over the course of her hospital stay.

It was not clear in this case whether the severe inflammatory myositis was a consequence of an acute viral inflammatory myositis due to SARS-CoV-2 or as part of MIS-C, which has been recently described. This patient did fulfil all the criteria for the diagnosis of MIS-C and was subsequently treated with intravenous immunoglobulin 2 g/kg, and methylprednisolone 10 mg/kg. Intravenous injection (IVI) for 3 days followed by 30 mg/kg for 2 days. Antibiotics were stopped after 72 hours as no organisms were cultured on blood, Cerebrospinal Fluid (CSF), urine or stool.

### OUTCOME AND FOLLOW-UP

Her inflammatory markers improved and were normal on discharge (table 1). She was discharged with residual muscle weakness, for which she continues to receive outpatient neurology follow-up visits and outpatient physiotherapy rehabilitation. Within 1 month of hospital discharge, she had returned to baseline premorbid function and is currently thriving physically and academically at school.

### DISCUSSION

Benign myositis following acute viral illness may occur as a self-limiting condition. It usually presents with a sudden onset of lower extremity pain and weakness during or following recovery from an acute viral illness. Rhabdomyolysis is a rare but described complication of viral myositis, particularly influenza A infections.

There has been one published case report in the paediatric literature of a 16-year-old boy who presented with acute SARS-CoV-2 infection, rhabdomyolysis and acute kidney injury, although MIS-C was not considered as a possible diagnosis. There have been other instances of benign myositis associated with SARS-CoV-2 infection reported in paediatric patients.

In adult patients infected with SARS-CoV-2, necrotising autoimmune myositis has been reported in up to 10% of SARS-CoV-2-infected patients. The clinical presentation of extremely high CK levels (>10000), associated myalgia and weakness is typical.

Elevated CK levels without associated rhabdomyolysis and acute kidney injury have also been reported in adult patients. There have also been reports in adult patients of SARS-CoV-2-associated autoimmune myositis presenting with elevated serum CK levels and acute kidney injury, although not requiring RRT. Delayed onset necrotising myositis, confirmed by muscle biopsy, has also been reported in an adult patient following an infection with SARS-CoV-2.

A wide range of SARS-CoV-2-associated neurological manifestations have been described in the current literature, ranging from benign anosmia, cranial nerve palsies, encephalopathy and acute inflammatory demyelinating polyradiculopathy, with one review documenting 11 cases of Guillain-Barré syndrome in several SARS-CoV-2 hotspots.

Recent research has shown that SARS-CoV-2 displays viral tropism and can invade tissues binding to the ACE2 receptor on certain host cells, mediated by its surface spike protein. The ACE2 receptor is primarily expressed in lung alveolar cells, small intestines enterocytes, vascular endothelial cells and renal cells, but is also expressed on glial cells and neurons. Additionally, the cytokine storm triggered in SARS-CoV-2 infection has been shown to cause inflammation of the blood–brain barrier and increases its permeability, exacerbating neuroinflammation leading to a wide array of associated neurological symptoms.

MIS-C is a severe complication of SARS-CoV-2 in children. The exact incidence is unknown; however, one report estimates the incidence of MIS-C to be 2 per 100 000 SARS-CoV-2-positive individuals who are younger than 21 years of age.

According to the WHO, six criteria must be met for the diagnosis of MIS-C:

- Age 0–19.
- History of fever for at least 3 days.
- Clinical evidence of multisystem involvement.
- Elevated inflammatory markers.
- No other obvious cause of overwhelming bacterial sepsis.
- Evidence of infection with SARS-CoV-2 (including serology or a positive contact).

Our patient fulfilled the diagnostic criteria for MIS-C and demonstrated clinical improvement on receiving intravenous immunoglobulin and corticosteroids. This, together with the low serum complement levels (C3 and C4), which subsequently normalised following clinical recovery and subsequent negative SARS-CoV-2 PCR test, indicates the possibility of an autoimmune aetiology for her inflammatory myositis.

A muscle biopsy was not done, but may have been useful to distinguish between necrotising myositis and inflammatory myositis.

### Table 1 Progression of the patient’s relevant blood results

<table>
<thead>
<tr>
<th>Day</th>
<th>Creatinine (mg/dL)</th>
<th>GFR (mL/min)</th>
<th>CRP (mg/L)</th>
<th>CK (U/L)</th>
<th>Ferritin (μg/L)</th>
<th>WCC (×10⁹/L)</th>
<th>Platelets (×10⁹/L)</th>
<th>D-dimer (mg/L)</th>
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<tr>
<td>0</td>
<td>248</td>
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<td>211</td>
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<td>30</td>
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<td>173</td>
<td>13</td>
<td>362</td>
<td>2.19</td>
</tr>
</tbody>
</table>

GFR was calculated with the Cockcroft-Gault equation.

CK, creatine kinase; CRP, C reactive protein; GFR, glomerular filtration rate; WCC, white cell count.

During my stay at the hospital, even though I could not walk, I felt like I was at home because there was enough care, the staff were there for me, treated me well and they came every single day to check on me.
Learning points

► While paediatric patients are often diagnosed with SARS-CoV-2 incidentally, multisystem inflammatory syndrome in children (MIS-C) is a well-documented complication and can lead to serious and often fatal complications.
► Severe inflammatory myositis, either as a direct result of SARS-CoV-2 multisystem involvement or as a secondary immune process (MIS-C), needs to be considered in a patient with elevated creatine kinase levels and muscle weakness as early treatment may prevent acute kidney injury.
► Further research, through muscle biopsies, in the setting of severe myositis with SARS-CoV-2 infection may be useful.

myositis. There are no studies or cases to date documenting muscle biopsies being done on SARS-CoV-2-infected patients, leading to a niche for urgent research into a possible autoimmune inflammatory myositis in the spectrum of SARS-CoV-2 manifestations.

Contributors FC contributed as primary author, corresponding author and selected the case for description. She also contributed to literature review and writing of the case report. AJS contributed as a primary author and was responsible for interpreting the case for description. She also contributed to literature review and writing of the report. SM acted as the overall supervisor for the case report. AJS contributed as a primary author and was responsible for interpreting the case for description. She also contributed to literature review and writing of the report. SM acted as the overall supervisor for the case report.

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