Paediatric inflammatory multisystem syndrome temporally associated with COVID-19: a new virus and a new case presentation

Phoebe Makiello, Sima Svirpliene, Lisa Finlay, Jean McKnight

SUMMARY
An 11-year-old boy presented with features resembling those described in health alerts on Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS), including persistent fever, haemodynamic instability and abdominal pain. Laboratory tests, including raised inflammatory markers, D-dimer, troponin and a coagulopathy, were consistent with PIMS-TS. Our patient required transfer to the paediatric intensive care unit; an echocardiography revealed left ventricular dysfunction. He was treated with intravenous immunoglobulins (Igs), corticosteroids and aspirin, with full resolution of clinical symptoms. A follow-up echocardiogram 1 month after discharge was unremarkable.

Three SARS-CoV-2 PCRs on respiratory samples, taken over the initial 4-day period, were negative, as was a SARS-CoV-2 PCR on faeces 1 month after presentation; titres of IgG were clearly elevated. The negative PCRs in the presence of elevated titres of IgG suggest that the inflammatory syndrome might have developed in a late phase of COVID-19 infection when the virus was no longer detectable in the upper airway.

BACKGROUND
The rapid spread of SARS-CoV-2, causing COVID-19 has led to a global pandemic. COVID-19 is thought to have a lower incidence in the paediatric population as only 2% of all reported cases occurred in patients under the age of 20 years. A recent systematic review of clinical features in 1065 PCR positive paediatric patients with SARS-CoV-2 found that the majority presented with mild symptoms: fever, dry cough and fatigue or were asymptomatic. Following reports of a number of children developing multisystem inflammation, with symptoms similar to those of Kawasaki Disease (KD), some of whom tested positive for COVID-19, the Paediatric Intensive Care Society issued a health alert on the 27 April 2020 and the Royal College of Paediatrics and Child Health (RCPCH) published treatment guidelines shortly thereafter.

We describe here the case of a paediatric patient treated for a multisystem inflammatory syndrome during the COVID-19 pandemic, who was tested with (RT-PCR) for SARS-CoV-2, three times on nasopharyngeal swabs and once on faeces, with negative results, but with positive immunoglobulin G (IgG) SARS-CoV-2 serology both before and after immunoglobulin administration. This case is published with parental permission.

CASE PRESENTATION
The patient is an 11-year-and-11-month-old white British boy, previously healthy and fully immunised (including influenza vaccinations), whose mother initially telephoned the general practitioner on the 26 April as he was vomiting, had lost his appetite and had an altered sense of taste, complaining that all food tasted ‘funny’; he had been feverish and feeling generally unwell and lethargic since 25 April. The UK government imposed a lockdown, including school closures from the evening of the 23 March and the patient had not left home for school or social gatherings since lockdown. No household contacts displayed any symptoms of COVID-19.

He was sent for a nasopharyngeal and throat swab, taken at the COVID-19 hub on 27 April. The patient presented through the emergency department on 28 April, complaining of a 3-day fever unresponsive to paracetamol, headache, sore neck and abdominal pain, with a new maculopapular rash on the right elbow. He was assessed in the paediatric unit where he was found to be tachycardic with a temperature of 39.8°C, with no focal signs of infection and no meningism. He initially complained of severe right iliac fossa pain and was tender to percussion in the lower abdomen. The patient did not complain of diarrhoea but was nauseated and had vomited for 3 days prior to admission. He exhibited no respiratory signs or symptoms. There was no conjunctival inflammation or lymphadenopathy. He was tachycardic, the rest of the cardiovascular examination was normal. An ECG recorded when his heart rate was 119 showed no evidence of arrhythmia; he was put on telemetry, which recorded further intermittent increases in heart rate up to 180 bpm.

On the 29 April, 25 hours following his initial admission to the paediatric department, it was observed that the patient had cracked lips; during the same examination, he was found to have developed a 2/6 systolic murmur audible over the entire precordium and was shocked with a heart rate of 129 bpm, a blood pressure of 82/48 and a tachypnoea up to RR 36, with oxygen saturations of 99% on air. He failed to respond to an initial 10 ml/kg 0.9% NaCl bolus. He received a dose of gentamicin and was started on 3 litres of oxygen through nasal canulae.

Due to his worsening cardiovascular status and laboratory results consistent with multisystem inflammation, and following the RCPCH guideline recommending early Pediatric Intensive Care Unit...
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(PICU) admission in such cases, a decision was made to transfer the patient to the Glasgow’s Royal Hospital for Sick Children PICU. He did not require ventilation or cardiovascular support, although his arterial blood gas on arrival (on 3 litres of oxygen) showed a partial pressure of oxygen of 5.5. The patient was monitored for a total of 34 hours in PICU and was thereafter fit to be discharged to a paediatric ward for continuation of therapy. His echocardiogram revealed mild left ventricular (LV) impairment but no evidence of coronary ectasia or valvular dysfunction. Following 5 days in the ward, he was fit to be discharged home with low dose aspirin and omeprazole to be taken until otherwise advised by the cardiologist, with an outpatient cardiology follow-up, including a repeat ECG and echography on 4 June. Both the ECG and the echography were normal, with the latter showing no evidence of aneurysms, valve impairment or heart failure. On cardiologist advice, the patient remains on low dose aspirin and will have a further follow-up appointment in 3 months’ time. Follow-up blood tests on 11 May (see tables 1 and 2) showed that he was no longer lymphopenic and his CRP had normalised to <3 mg/dL; his D-dimer was no longer elevated having decreased to 351 ng/mL on 5 May, by which date his clotting screen had also normalised.

INVESTIGATIONS
A nasopharyngeal swab and throat swab, taken at the COVID-19 hub on 27 April, tested negative for SARS-CoV-2. A second nasopharyngeal swab, taken at the Dumfries and Galloway Royal Infirmary (DGRI) on 29 April, was also negative for SARS-CoV-2, as was a further swab taken in Glasgow on 30 April. All virology studies (PCRs as well as EBV serology) were negative. His blood cultures showed no growth (see table 3).

Initial laboratory investigations on 28 April included a urinalysis that was positive for microscopic haematuria and protein.

Table 1  Laboratory test results, biochemistry

<table>
<thead>
<tr>
<th></th>
<th>28 April 2020</th>
<th>29 April 2020</th>
<th>30 April 2020</th>
<th>01 May 2020</th>
<th>02 May 2020</th>
<th>05 May 2020</th>
<th>11 May 2020</th>
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<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>13</td>
<td>11</td>
<td>13</td>
<td>6</td>
<td>8</td>
<td></td>
<td></td>
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<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>116</td>
<td>92</td>
<td>91</td>
<td>109</td>
<td>105</td>
<td></td>
<td></td>
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<tr>
<td>ALT (IU/L)</td>
<td>17</td>
<td>12</td>
<td>13</td>
<td>32</td>
<td>40</td>
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<tr>
<td>AST (IU/L)</td>
<td>21</td>
<td>19</td>
<td>19</td>
<td>47</td>
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<td></td>
<td></td>
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<tr>
<td>Gamma GT (IU/L)</td>
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<td>15</td>
<td>15</td>
<td></td>
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<td></td>
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<tr>
<td>Sodium (mEq/L)</td>
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<td>135</td>
<td>134</td>
<td>134</td>
<td>139</td>
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<td></td>
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<tr>
<td>Potassium (mEq/L)</td>
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<td>3.7</td>
<td>3.9</td>
<td>4.1</td>
<td>4.7</td>
<td></td>
<td></td>
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<tr>
<td>Urea (mmol/L)</td>
<td>4.3</td>
<td>2.3</td>
<td>2.3</td>
<td>4.5</td>
<td>4.6</td>
<td></td>
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<tr>
<td>Creatinine (μmol/L)</td>
<td>37</td>
<td>36</td>
<td>34</td>
<td>34</td>
<td>31</td>
<td></td>
<td></td>
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<tr>
<td>CRP (mg/dL)</td>
<td>155</td>
<td>174</td>
<td>206</td>
<td>185</td>
<td>93</td>
<td>20</td>
<td>&lt;3</td>
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<tr>
<td>Procalcitonin (ng/mL)</td>
<td>3.16</td>
<td>292</td>
<td>323</td>
<td></td>
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<tr>
<td>Ferritin* (ng/mL)</td>
<td>292</td>
<td>323</td>
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<td></td>
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<tr>
<td>Cardiac troponin T† (ng/L)</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ANA screen</td>
<td>Negative</td>
<td></td>
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</tbody>
</table>

* reference range 13–300 ng/mL
† reference range 0–13 ng/mL
ALT, Alanine aminotransferase; ANA, Anti-nuclear and centromere Antibodies; AST, Aspartate aminotransferase; CRP, C-reactive protein; Gamma GT, Gamma-Glutamyltransferase.

Table 2  Laboratory test results, haematology

<table>
<thead>
<tr>
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<th>28 April 2020</th>
<th>29 April 2020</th>
<th>01 May 2020</th>
<th>05 May 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/L)</td>
<td>126</td>
<td>121</td>
<td>104</td>
<td>118</td>
</tr>
<tr>
<td>White blood cells (x1000/mm3)</td>
<td>10.0</td>
<td>9.9</td>
<td>8</td>
<td>16.6 *</td>
</tr>
<tr>
<td>Red blood cells (x1,000,000/mm3)</td>
<td>4.70</td>
<td>4.37</td>
<td>3.78</td>
<td>4.25</td>
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<tr>
<td>Haematocrit (%)</td>
<td>37.0</td>
<td>34.0</td>
<td>30.5</td>
<td>36.2</td>
</tr>
<tr>
<td>Mean cell volume (fL)</td>
<td>79</td>
<td>79</td>
<td>80.7</td>
<td>85.2</td>
</tr>
<tr>
<td>Platelets (x1000/mm3)</td>
<td>230</td>
<td>220</td>
<td>295</td>
<td>712 *</td>
</tr>
<tr>
<td>Neutrophils (x10³ cells/μL)</td>
<td>8.9</td>
<td>8.8</td>
<td>7</td>
<td>11.6 *</td>
</tr>
<tr>
<td>Lymphocytes (x10³ cells/μL)</td>
<td>0.8</td>
<td>0.7</td>
<td>0.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Monocytes (x10³ cells/μL)</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Eosinophils (x10³ cells/μL)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.0</td>
<td>0.19</td>
</tr>
<tr>
<td>Basophils (x10³ cells/μL)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>PT (s)</td>
<td>16.7</td>
<td>18</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.2</td>
<td>1.5</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>APTT (s)</td>
<td>36.7</td>
<td>34</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen level (g/L)</td>
<td>6.42</td>
<td>5.9</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>D-dimer (ng/mL)</td>
<td>3850</td>
<td>927</td>
<td>351</td>
<td></td>
</tr>
</tbody>
</table>

* After steroid administration.
† reference range 9–13
‡ reference range 0–500 ng/mL Fibrinogen Equivalent Units (FEU)
APTT, Activated Partial Thromboplastin Time Test; INR, International Normalized Ratio; PT, Prothrombin Time.
Urea and electrolytes and a full blood count were normal and remained so. The patient’s CRP was 155 and he was lymphopenic.

A chest X-ray performed on 29 April showed streaky changes bilaterally. Following clinical deterioration on 29 April, blood tests were ordered in order to confirm inflammatory multisystem syndrome (see tables 1 and 2). These showed raised inflammatory markers, including procalcitonin (3.16 ng/mL), CRP (174 mg/dL) and a fibrinogen level (6.42 g/L). His cardiac troponin T was 100 ng/L. His D-dimer was 3850 ng/mL. His clotting screen was abnormal with increased values, including APTT of 1.3 and a PT of 16.7 seconds. Liver function tests were normal (see tables 1 and 2).

A SARS-CoV-2 PCR on faeces produced on 26 May (31 days following initial presentation) was negative; this does not rule out an infection with COVID-19 as it is estimated that a patient might shed virus particles up to 40 days after infection, and we do not have an accurate timeframe for the possible period of infection.

IgG serology performed on serum samples collected on 28 April, prior to Ig administration as well as on 2 June, after intravenous Ig treatment were clearly positive. The Abbott SARS-CoV-2 IgG assay was used (on the Architect instrument), which was found in the recent Public Health England evaluation to have a specificity of 100% (95% CI: 97.79 to 100).

**DIFFERENTIAL DIAGNOSIS**
Appendicitis was initially suspected, due to the severe right iliac fossa pain. When reviewed by the surgical team, however, the patient was no longer tender and surgeons ruled that the abdominal pain was unlikely due to any surgical cause. The combination of symptoms: intractable fever lasting 5 days, severe abdominal pain, rash, cracked lips, cardiovascular instability and characteristic blood results led, on 29 April, to a presumptive diagnosis of Paediatric Inflammatory Multisystem Syndrome Temporarily associated with SARS-CoV-2 (PIMS-TS) (also known as Multisystem Inflammatory Syndrome in Children (MIS-C) in the USA) with possible multi-organ failure, despite a previous negative SARS-CoV-2 RT-PCR on 27 April.

**TREATMENT**
The patient initially received empirical cefotaxime and metronidazole due to the suspicion of a surgical abdomen. He was definitively treated on 30 April with 2 g/kg intravenous Ig’s, which terminated his fevers, and completed a 5-day course of intravenous methylprednisolone. Cefotaxime and metronidazole were also continued for 5 days.

**OUTCOME AND FOLLOW-UP**
The patient was monitored for a total of 34 hours in PICU and was thereafter fit to be discharged to a paediatric ward for continuation of therapy. His echocardiogram revealed mild LV impairment but no evidence of coronary ectasia or valvular dysfunction. Following 5 days in the ward, he was fit to be discharged home with low dose aspirin and omeprazole to be taken until otherwise advised by the cardiologist, with an outpatient cardiology follow-up, including a repeat ECG and echography on 4 June. Both the ECG and the echography were normal, with the latter showing no evidence of aneurysms, valve impairment or heart failure. On the cardiologist’s advice, the patient remains on low dose aspirin and will have a further follow-up in 3 months’ time. Follow-up blood tests on 11 May (see tables 1 and 2) showed that he was no longer lymphopenic and his CRP had normalised to <3 mg/dL; his D-dimer was no longer elevated having decreased to 351 ng/mL on 5 May, by which date his clotting screen had also normalised.

**DISCUSSION**

The precise aetiology of multisystem inflammatory syndromes, which includes KD, is still a matter of some debate. The most widely accepted hypothesis proposes an aberrant response of the immune system to as yet unidentified pathogens in genetically predisposed individuals. It is possible that KD may be triggered by or co-exist with an infection. More specifically, an RNA virus usually causing asymptomatic infection in a host not previously exposed to the virus has been proposed as the trigger for KD in susceptible individuals. An association between coronaviruses and KD remains a matter of debate. Whether PIMS-TS (also referred to in the literature as MIS-C) and KD constitute the same entity is currently not ascertained. Although they share some clinical similarities, their epidemiology is quite dissimilar. As there is no diagnostic test for either condition, it remains difficult to distinguish between the two.

Although gastrointestinal symptoms such as nausea, vomiting and diarrhoea were reported in a few cases, in particular in a
newborn and infants, prior to the recent reports of multisystem inflammatory syndrome, abdominal pain such as experienced by our patient had not been a clinical feature reported in the literature on COVID-19 in children. However, in a table summarising details of children presenting with hyperinflammatory shock during the COVID-19 pandemic, abdominal pain featured in 6 out of 8 cases, with a further patient suffering from vomiting and diarrhoea and in a prospective observational study of 21 children with PIMS-TS, 100% experienced gastrointestinal symptoms and 95% suffered from acute abdominal pain.

Cardiac inflammation, defined as myocarditis with raised troponin and NT-proBNP, is a common feature of this presentation. There is also a mention of cases developing an appearance on their coronary arteries consistent with KD, and out of eight cases in London, all patients had a raised troponin (from 25 ng/L to 675 ng/L) and seven out of eight had evidence of cardiac impairment, ranging from mild to severe, on echocardiogram. Similarly, our patient presented with an elevated troponin; an inpatient echocardiography demonstrated mild LV impairment, with a follow-up echocardiography 1 month later showing no impairment and a plan to continue low dose aspirin and a repeat echocardiogram in 3 months. When coronary involvement appears in KD, it typically occurs after the initial presentation, hence the necessity for further monitoring, including a repeat echocardiogram.

Three COVID-19 RT-PCR tests on nasopharyngeal and throat swabs performed within a 4-day period were negative. Several negative results do not exclude the diagnosis of PIMS-TS; indeed, the RCPCH guideline requires only the absence of potential causative organisms other than SARS-CoV-2. Accordingly, in various reports of PIMS-TS cases, a majority of patients initially tested negative for SARS-CoV-2 on respiratory sample RT-PCR, with some subsequently positive on either repeat RT-PCR or serology. Although the most commonly used RT-PCR test for SARS-CoV-2 in Europe has a reported in vitro sensitivity of 95% (CI: 2.8 to 8.0), in vivo sensitivity has been much lower. Indeed, a study of 1070 specimens collected from 205 patients with COVID-19 in China records the in vivo sensitivity of the RT-PCR for nasal swabs as 63% and that for pharyngeal swabs as 32%. An additional factor affecting the detection of SARS-CoV-2 in respiratory samples is the timing of the sampling. Indeed, a cohort study determined that salivary viral load was highest during the first week after symptom onset and subsequently declined over time, whereas, overall, viral load was found to be correlated with older age. There is, however, a lack of clear data on these important questions at present, in particular where children are concerned. It is, therefore, crucial not to exclude cases with clinical symptoms on the grounds of a negative SARS-CoV-2 PCR, as this might lead to underestimation of disease burden and risk delaying diagnosis and targeted management.

Recent in vitro experiments have demonstrated that intestinal epithelium supports SARS-CoV-2 replication. As there is some evidence that patients may shed SARS-CoV-2 in their stools up to 40 days after initial infection, it is reasonable to consider SARS-CoV-2 PCR on stool samples. Indeed, a recent article reported that eight paediatric patients with COVID-19 tested positive on rectal swabs, even after nasopharyngeal testing was negative, although this trend is as yet to be confirmed by large studies. The sensitivity of RT-PCR on faeces was reported as 29% (44 out of 153 specimens in patients known to have COVID-19). In a different study, PCR positivity in stool was observed in 55 out of 96 (57%) infected patients, and remained positive for a median duration of 22 days (IQR: 17–31 days), and was unrelated to clinical severity. It is advisable to perform the PCR on stool while the patient is still experiencing symptoms; in our case, this was delayed due to the unavailability of the test at that time.

The Abbott SARS-CoV-2 IgG assay, used for our patient, has a reported sensitivity of 93.3% for samples collected ≥14 days after symptom onset and may, therefore, detect cases missed on RT-PCR. Although many of the reported PIMS-TS cases, including our patient, are positive for SARS-CoV-2 IgG and test negative for the nasopharyngeal and throat RT-PCR assays, this does not necessarily entail that PIMS-TS is a post-infectious phenomenon and not the result of an acute infection. Indeed, as in our case, many children experience primarily gastroenterological rather than respiratory symptoms, and few have been tested with an RT-PCR on faecal sample. In our patient, IgG titres were already raised on day 3 after symptom onset (including aegusia, which has been associated with COVID-19 infection, but is nonetheless relatively non-specific). Given the sensitivity of 53.1% at 7 days after symptom onset and 82.4% at 10 days, it is possible that the assay is able to detect IgG during the acute phase. The possibility that PIMS-TS constitutes a post-infection syndrome cannot, however, at present be excluded. Another interesting hypothesis concerning its pathogenesis relates to delayed type I and type III interferon responses leading to slow viral clearance and cytokine storm.

The positive SARS-CoV-2 serology alongside clinical features typical of other children presenting with multisystem inflammatory syndromes, a number of whom also tested positive on SARS-CoV-2 RT-PCR, increases the possibility of this presentation being linked causally, by a pathogenetic mechanism as yet not fully ascertained, to COVID-19.

Learning points

► Acute gastrointestinal pain in the context of persistent fever during the COVID-19 pandemic should lead to suspicion of multi-system inflammatory syndrome in children.
► Cardiac inflammation is a feature of this presentation.
► It appears that early treatment with immunoglobulins (Igs) and intravenous steroids is helpful.
► Negative SARS-CoV-2 PCR tests do not exclude COVID-19 and SARS-CoV-2 IgG serology ought to be performed.
► PCR on faeces should be considered early on, in particular in cases presenting with mainly gastrointestinal symptoms.

Acknowledgements

Thank you to the patient and his family for their willingness to share this case. Thank you also to all members of the healthcare teams in Dumfries and Glasgow who contributed to the care of the patient discussed in this case report. We wish to acknowledge Dr Moira Thomas and her team, Clinical lead for Immunology and Neuroimmunology at the Queen Elizabeth University Hospital in Glasgow, for performing and interpreting the SARS-CoV-2 immunoglobulin G serology.

Contributors

PM conceived the report and provided over all leadership of the project. PM and SS wrote the manuscript, with input from LF and JMK. All authors participated in the patient’s care. The patient was under the care of JMK.

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Parental/guardian consent obtained.

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**REFERENCES**