Case report

Paediatric case of prolonged COVID-19 manifesting as PMIS-TS and atypical Kawasaki

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SUMMARY
The COVID-19 pandemic has created an unprecedented disease burden worldwide, affecting patients of all ages. Recently, there has been a rise in a new inflammatory condition termed paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PMIS-TS). We are yet to understand significant risk factors, disease progression and prognosis in children affected. We describe a case of a 9-year-old boy who tested positive concurrently for the SARS-CoV-2 virus 4 weeks apart. He presented with a 2-day history of fever, abdominal pain, headache and diarrhoea. Initial investigations supported PMIS-TS and he went on to develop atypical Kawasaki disease. With no results to differentiate between his positive results, we question whether he remained positive throughout or recovered with reactivation of the virus. There are reports of reactivation in adults but none in children. There are also no reports of children remaining positive for such a prolonged period, which raises public health concerns.

BACKGROUND
Since the beginning of the COVID-19 outbreak, the morbidity and mortality rates in children have been significantly lower in comparison to adults.1 2

However, emerging case reports in the UK indicate an alternate inflammatory response exclusive to children. This has been termed paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PMIS-TS).

The condition shares features of atypical Kawasaki disease and toxic shock syndrome, including a persistent fever with multiorgan involvement (gastrointestinal, cardiac, renal, respiratory, haematologic, shock or neurological disorder), inflammation (neutrophilia, elevated C reactive protein (CRP) and lymphopenia) and additional features, for example, abdominal pain, rash, conjunctivitis, diarrhoea and vomiting.3- 14

Subsequently, there have been national alerts in both the UK and the USA calling for early assessment, management and specialist referral of children presenting with this unusual clinical picture.5 6

CASE PRESENTATION
A previously fit and well 9-year-old, white Caucasian boy was referred to the paediatric team for assessment. He had a body mass index (BMI) on the 98th centile with a medical history of well-controlled asthma.

The patient tested positive for the SARS-CoV-2 virus, on an oropharyngeal swab, 4 weeks prior to admission when he suffered with mild symptoms (headache, fever, cough) for 2 days. Both key worker parents also tested positive at this time, while his 12-year-old brother remained asymptomatic. The patient remained asymptomatic for the following 4 weeks, until his admission to hospital.

He presented with a 2-day history of pyrexia >38.0°C, headache, neck pain, abdominal pain and diarrhoea. He had been swabbed for a second time in community on day 1 of symptoms, the result of which was confirmed to be positive on arrival at hospital.

On examination, the patient showed no signs of cardiorespiratory disease. Neurological examination was unremarkable. His abdomen was soft with no organomegaly, but he had some tenderness in the periumbilical region. There were no dermatological findings and no subcutaneous oedema present. On admission, his temperature was 37.4°C, heart rate 104 beats/min, respiratory rate 22 breaths/min, blood pressure 110/58 mm Hg and saturations 97% in air.

INVESTIGATIONS
On his initial bloods (see table 1), his full blood count showed a raised white cell count (11.5×10^9/L) with neutrophilia (10.1×10^9/L) and lymphopenia (0.8×10^9/L); biochemistry revealed a raised CRP (351 mg/L), D-dimer (1234 ng/mL) and LDH (376 U/L); coagulation screen demonstrated an abnormal fibrinogen (11.3 g/L); and a blood gas showed a metabolic acidosis with pH (7.33), pCO₂ (5.6 kPa), bicarbonate (22 mmol/L), base excess (−4.7 mEq/L) and lactate (3 mmol/L). A chest radiograph was normal.

On day 2, he presented with episodes of palpitations. An ECG showed a sinus tachycardia at 130 beats/min. In addition, his blood tests showed improvement (see table 1): CRP (267 mg/L), white cell count (10.8×10^9/L) with neutrophils (9.6×10^9/L) and fibrinogen (9.3 g/L).

By day 3, the patient’s predominant complaint was of on-going abdominal pain, which raised concern of a perforated appendix. Following a surgical review, an ultrasound scan of his abdomen demonstrated bowel wall thickening with inflammatory changes, but the appendix was not seen. He underwent a CT abdomen, which showed terminal ileitis with mesenteric adenitis and bilateral pleural effusions. A repeat chest radiograph showed...
progressive patchy areas of pulmonary infiltrate throughout the mid zones.

Having had little clinical improvement and with ongoing inflammatory changes, we believed we were dealing with an evolving multisystem inflammatory syndrome.

Therefore, on day 3, he was discussed with our tertiary centre gastroenterology team and infectious diseases department. Blood results worsened over day 3 and 4 of admission (see table 1); CRP (310 mg/L), D-dimer (2531 ng/mL), LDH (492 U/L) and fibrinogen (11.3 g/L). A lumbar puncture was performed as advised and he was transferred for further investigation and management on day 4, when a bed was available, for review by the infectious disease and rheumatology teams.

At the tertiary centre, his bloods showed a rise in his cardiac inflammatory markers (see table 1); D-dimer (2531 ng/mL), LDH (492 U/L) and fibrinogen (9.9 g/L). A lumbar puncture was performed as advised and he was transferred for further investigation and management on day 4, when a bed was available, for review by the infectious disease and rheumatology teams.

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The patient’s most significant symptom was worsening peri-umbilical abdominal pain. Since the abdominal ultrasound scan demonstrated a thickened bowel wall, a second review by the surgical team was requested to investigate for an acute surgical abdomen. Although this was excluded with a CT abdomen, there was evidence of inflammation within the lymph nodes and confirmed thickening of the bowel wall.

These radiological findings coupled with his biochemical markers portrayed a clear picture of an evolving inflammatory process secondary to COVID-19. Although viral induced macrophage activation syndrome and haemophagocytic lymphohistiocytosis are important differentials, he did not meet the classification criteria. A complete sepsis screen ruled out any superimposed bacterial infection with urine, cerebrospinal fluid, stool and blood cultures all negative. His initial reduction in CRP following treatment with antibiotics was falsely reassuring. His ongoing inflammatory changes (raised CRP and doubling D-dimer) with no clinical improvement prompted discussion with the tertiary centre and subsequent transfer was arranged. A multidisciplinary team (MDT) discussion between the rheumatology and infectious diseases teams, locally and from another tertiary centre, concluded that an ongoing inflammatory process with fever for 7 days, elevated inflammatory markers and positive COVID-19 test a month prior to admission made a paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PMIS-TS) highly likely. As the patient showed coronary artery anomalies and was noted to now have conjunctival injection of one eye (day 4 of admission), he was considered to belong more to the ‘atypical’ Kawasaki-disease spectrum of this hyperinflammatory syndrome. This was further evident with defervescence following a single dose of intravenous immunoglobulin.

**DIFFERENTIAL DIAGNOSIS**

The initial impression was of acute viral illness secondary to active SARS-CoV-2 virus, labelled COVID-19.

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**TREATMENT**

On consideration of his admission blood tests, he was treated with intravenous ceftriaxone and clarithromycin was added to treat a suspected atypical infection. He required fluid resuscitation of 20 mL/kg 0.9% normal saline with maintenance intravenous fluids to maintain adequate blood pressure. Metronidazole was added on day 2 to cover for an acute abdomen. On day 3 of admission, he suffered acute respiratory distress, requiring minimal oxygen supplementation of 1–2 L/min via face mask intermittently.

At the tertiary centre, following an echocardiogram and an MDT discussion, he was given a single dose of intravenous immunoglobulins (2 g/kg), started on intravenous methylprednisolone (30 mg/kg) and commenced on low-dose aspirin (5 mg/kg). His temperatures settled following intravenous immunoglobulin and he reported feeling significantly better within the following 24 hours.

He was discharged home on aspirin, weaning dose of prednisolone and omeprazole 12 days after his initial presentation.

### Table 1: Summary of blood results during inpatient admission

| Request                  | Range     | Day 1      | Day 2      | Day 3      | Day 4      | Day 5      | Day 6      | Day 8      |
|--------------------------|-----------|------------|------------|------------|------------|------------|------------|------------|
| White cell count (x10^3/L) | 4–11      | 11.5       | 10.8       | 4          | 11         |            |            |            |
| Haemoglobin (g/L)        | >130      | 128        | 113        | 130        | 111        |            |            |            |
| Platelets (x10^9/L)      | 150–400   | 236        | 257        |            |            |            |            |            |
| Neutrophils (x10^9/L)    | 2–7.5     | 10.1       | 9.6        |            |            |            |            |            |
| Lymphocytes (x10^9/L)    | 1.3–3.5   | 0.8        | 0.6        | 0.3        | 1.5        |            |            |            |
| CRP (mg/L)               | 0–5       | 351        | 267        | 310        | 295        | 239        | 70         |
| Fibrinogen (g/L)         | 1.8–3.5   | 11.3       | 9.3        | 9.9        | 6          | 3.6        |            |            |
| D-dimer (ng/mL)          | <500      | 1234       |            | 2531       | 2754       | 3198       | 3002       |
| LDH (U/L)                | 140–280   | 376        |            | 492        | 340        |            |            |            |
| Triglycerides (mmol/L)   | 0.4–1.4   |            |            |            |            |            |            | 1.0        |
| Ferritin (ng/mL)         | 12–300    | 217        |            | 393        |            |            |            | 297        |
| Troponin (ng/L)          | 0–14      |            |            |            | 85         |            |            | 27         |
| NT-proBNP (ng/L)         | <400      |            |            | 10506      |            |            |            | 4447       |
| Total 25-hydroxyvitamin D (nmol/L) | >50 |            |            |            |            |            |            | 51         |

CRP, C reactive protein; LDH, Lactate dehydrogenase; NT-proBNP, N-terminal pro B-type natriuretic peptide.
OUTCOME AND FOLLOW-UP
Following his discharge from hospital, the patient was readmitted 4 days later with episodes of palpitations at home lasting <1 min. He had a normal ECG, his bloods were unremarkable and he was discharged home. He was seen 4 days later in clinic for his planned follow-up with normal observations and clinical examination. He reported feeling back to his normal self with no further episodes of palpitations.

One week later (2 weeks from initial discharge), he was reviewed by the cardiology team at the tertiary centre with a normal echocardiogram and ECG. He is waiting to have a 24-hour Holter monitoring at home and will remain on aspirin until further cardiology follow-up.

DISCUSSION
As of 15 May 2020, there have been a total of 230 suspected cases of PMIS-TS reported in European Union/European Economic Area countries and the UK in 2020. This patient presented similar to the cluster of initial nine children in the UK; with persistent fever and gastrointestinal symptoms. Since then national guidelines have suggested a diagnosis of PMIS-TS in any child presenting with: a persistent fever, inflammation and evidence of single-organ or multiorgan dysfunction, fulfilling partial or full criteria for Kawasaki disease, in whom a microbial cause has been ruled out and SARS-CoV-2 PCR testing is either positive or negative.

Aetiology for Kawasaki disease remains unknown and as yet, no definitive working hypothesis for its pathogenesis with PMIS-TS has been suggested. Reports have suggested obesity is significantly associated with disease severity in children affected by COVID-19. While more robust data are needed to confirm this link, it is a recognised risk factor in our patient. Although the probability of PMIS-TS is deemed to be low, its impact is assessed to be high. Therefore, we reiterate the importance of discussing suspected cases with tertiary specialists to ensure prompt treatment (infectious diseases, cardiology, rheumatology).

Unfortunately, there are no swabs in between the 4-week period when our patient tested positive for SARS-CoV-2 on two separate swabs. There are no reports of reactivation in children currently, neither are there reports of prolonged illness lasting 4 weeks. It is proposed that PMIS-TS is a postinfective, delayed antibody-mediated dysregulated immune response, with an onset between 2 and 4 weeks after initial infection. Further reports suggest prolonged duration of viral shedding in children with symptomatic infection. This case and others presenting similarly would pose significant public health concerns, although further monitoring is required to fully understand viral shedding in children.

We believe it is important for us as physicians to remain alert during this pandemic; sharing our experiences, keeping updated and keeping educated on the evolving case definitions and guidelines provided on COVID-19 in children.

Contributors MM, SM and NR all tended to the patient while on the ward and prior to transfer. MM and NR went on to follow-up the patient in an outpatient clinic appointment. MM wrote the abstract and case report. NR and SM read and reviewed the case report.

Funding This study was funded by Betsi Cadwaladr University Health Board; grant number (6195759).

Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Patient’s perspective
I felt very sad when I was ill and was glad that my mum was with me in hospital all the time. The doctors and nurses helped me get better, which has made me really happy. The medicine I had for the Kawasaki like disease when I was asleep stopped the awful headaches and tummy pains and I started to feel better. That day I felt like eating again and watching TV. I have had slight headaches since leaving hospital and pains in my ankle and knee joints. I have also been tired but I am starting to do more exercise each week. The doctors and nurses were great and looked after me very well. I really enjoyed the hospital food. When I felt better, I would have liked to have gone out for a walk around the ward but due to COVID-19 this was not possible. I did not like the needles but my blood needed to be taken, which I understood. I am very glad to be back home and I feel much better.

Mum: The whole situation was stressful. My husband was not allowed to be with me and at times I felt isolated and the worry and pressure was all on my shoulders. I felt emotionally and mentally drained, but once it became evident that my son was improving, I felt better in myself. I put my faith in the medical staff and they looked after my son in the best possible way in the circumstances; we are grateful for the support we have received.

Learning points
► Think about paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PMIS-TS) in children with prolonged fevers, and even those with a few days of fever with no clear focus and not responding to antimicrobial treatment.
► Although our case highlights a positive swab 4 weeks prior to admission, PMIS- TS should be considered irrespective of a previous or currently positive swab.
► This case demonstrates the challenges of PMIS-TS in a district general hospital and the importance of timely multidisciplinary team discussion with tertiary centres to guide effective treatment.
► Remember atypical Kawasaki and think about coronary artery involvement while investigating appropriately and in a timely manner.

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