

# Difficult acute lymphoblastic leukaemia diagnosis in a paediatric patient with mixed presentation of COVID-19 acute respiratory failure and multisystemic inflammatory syndrome

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## SUMMARY

New diagnoses of leukaemia and other malignancies are recently being made in paediatric patients with COVID-19. The rates of mortality and morbidity in some of these children are expected to be higher. In new cases, concurrent diagnosis can be difficult because multisystemic inflammatory syndrome (MIS-C) and malignancies have similar clinical presentations. We present the case of a preteenage child where the diagnosis of leukaemia was complicated and delayed by a multisystem involvement and an inconclusive bone marrow study. Clinical teams managing children with COVID-19 and MIS-C should suspect leukaemia and other malignancies when the clinical course is complicated and bone marrow suppression is persistent. Prompt diagnosis will allow start of treatment on time, minimising complications.

## BACKGROUND

Mortality of children with cancer has been reported to be between 2.7% and 5.3%.<sup>1–3</sup> There are no trials showing if the morbidity and mortality associated with viral infections in this specific population can be reduced by any specific treatment. These patients are at high risk of immunosuppression due to viral bone marrow suppression. In addition, the concern for immunosuppression secondary to chemotherapy has resulted in delayed or modified therapeutic schemes.<sup>4,5</sup> Currently, there are no specific recommendations for modified chemotherapy in patients with a diagnosis of acute lymphoblastic leukaemia (ALL) and SARS-CoV-2. More recently, cancer and multisystemic inflammatory syndrome (MIS-C) share clinical and laboratory features. When they occur simultaneously, early cancer diagnosis can be challenging, resulting in delayed therapies and putting patients at higher risk of complications. There is limited information on paediatric patients with ALL and MIS-C. We present the case of a preteenage child initially admitted with COVID-19 acute respiratory distress and later developed an inflammatory disease that was thought to be MIS-C but turned out to be ALL.

## CASE PRESENTATION

We present the case of a previously healthy preteenage child with a 3-day history of fever and

respiratory distress, with no other symptoms. The patient's father had COVID-19. On evaluation at a local emergency department, altered mental status, pallor, cold extremities and increased work of breathing were noticed. Vital signs showed a heart rate of 168 beats per minute, oxygen saturation of 82% on non-rebreather oxygen mask (15 liters per minute), blood pressure of 68/30 mm Hg and respiratory rate of 30 breaths per minute. Arterial blood gas showed hyperchloraemic metabolic acidosis, partial pressure of oxygen (PaO<sub>2</sub>) to inspired fraction of oxygen (FiO<sub>2</sub>) ratio of <100 and lactic acid of 10 mmol/L. The results of IgG and real-time reverse transcription polymerase chain reaction SARS-CoV-2 tests were positive. The team proceeded to intubate the patient and started mechanical ventilation and an epinephrine drip. On mechanical ventilation, the patient's oxygenation index was 6. The patient was admitted to paediatric critical care.

## INVESTIGATIONS

On admission, laboratory results support the diagnosis of MIS-C: C-Reactive protein (CRP) of 18 mg/L and a complete blood count (CBC) remarkable for severe pancytopenia. Leucocyte count was  $2.8 \times 10^9/L$ , haemoglobin was 63 g/L, haematocrit was 20% and platelet count was  $54 \times 10^9/L$ . Coagulation profile was within normal limits and the Coombs test was positive. A differential viral panel was sent, including complete hepatitis test, Cytomegalovirus (CMV) and Epstein barr virus (EBV), all negative for acute infection. An echocardiogram done on admission showed an ejection fraction of 45%, a cardiac index of 5.6 L/min and collapsed inferior vena cava. No diastolic dysfunction or signs of pulmonary hypertension were reported. A chest CT revealed pulmonary parenchymal disease with irregular ground-glass infiltrates with an alveolar pattern, predominantly on the right lung, in three lobes (figure 1). Troponin I on admission was 2.18 ng/mL (reference <0.01 ng/mL).

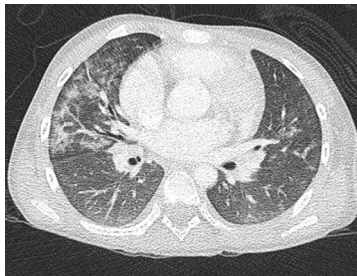
## DIFFERENTIAL DIAGNOSIS

The primary diagnosis was an acute COVID-19 respiratory failure with moderate acute respiratory distress syndrome (ARDS) complicated by septic shock versus cardiogenic and possible myocarditis. The differential was MIS-C based on inflammatory



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**Figure 1** Chest CT with contrast. Lung parenchyma shows ground-glass opacities with associated alveolar pattern, with predominant peripheral infiltrates.

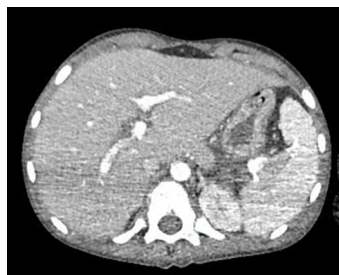
predominance and severe pancytopenia. Leukaemia was considered part of the initial differential due to the CBC findings, and a bone marrow study was planned if there was no improvement with initial therapy.

### TREATMENT

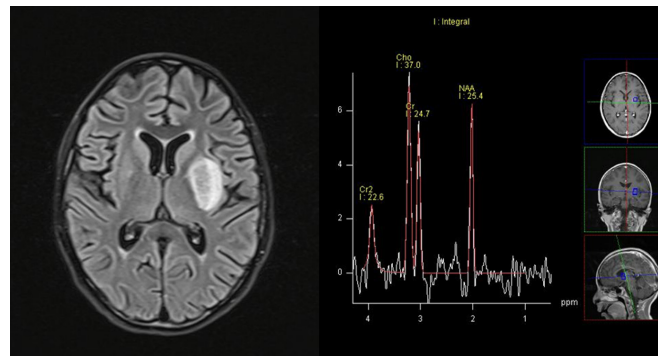
The patient was admitted to paediatric intensive care unit (PICU) on mechanical ventilation, vasopressors and inotropic support. Packed red blood cells were transfused. MIS-C therapy including intravenous immune globulin (IVIG) 2 g/kg/dose and methylprednisolone 4 mg/kg/day for 4 days was started. Vasopressors included epinephrine and norepinephrine titrated to a normal mean arterial pressure goal for age and height.

### OUTCOME AND FOLLOW-UP

In critical care, the patient's lactate cleared to 1.2 mmol/L after fluid and vasopressor therapy. During the first 5 days, there was an improvement in respiratory failure and the ventilator was weaned off. We obtained N-terminal pro B-type natriuretic peptide on day 3 of admission, which was mildly elevated at 216 pg/mL (reference <150 pg/mL). However, the inflammatory markers and pancytopenia persisted. A bone marrow aspirate was performed before extubation and showed 30%–50% cell lines, mainly erythroid line, in various stages of differentiation, and a myeloid line without mature forms and blasts. Clusters of dysmorphic megakaryocytes were present. Fibrosis and necrosis were noted in the bone marrow. This study was performed after treatment with IVIG and methylprednisolone. The findings were attributed to COVID-19. On day 7 of admission, the patient presented severe diffuse abdominal pain. Pancreatic enzymes were elevated and the team diagnosed pancreatitis. Cardiac enzymes were repeated, with mild elevation of troponin I to 0.036 ng/mL (reference <0.01 ng/mL). An abdominal CT confirmed pancreatitis of Balthazar B and C stage, with enlargement and inflammatory changes in the pancreas and peripancreatic fat (figure 2).



**Figure 2** CT of the abdomen with contrast showing suspected pancreatitis with inflammation of the peripancreatic fat, with no necrosis seen.



**Figure 3** Brain MRI and spectroscopy. Hyperintense lesions (T2) on the left basal ganglia. Spectroscopy shows a predominant total choline peak (Cho). Cr, creatine; Cr2, creatinine second peak; NAA, N-acetyl aspartate; PPM, parts per million.

On neurological examination, right hemiparesis was noted, progressing to quadriparesis. A brain CT showed left basal ganglia hypodensity with contrast enhancement. The deficit on the right side was worst, with decreased muscle strength, spasticity, hyper-reflexia and positive Babinski sign on the right foot. The suspected diagnosis was necrotising encephalitis secondary to COVID-19. An MRI study was performed revealing bilateral lenticular lesions, worst on the left side and on the left caudate nucleus (figure 3). MRI spectroscopy showed a spike in total choline (tCho) peak, interpreted as a sequela of encephalitis. We did not obtain a cerebrospinal fluid (CSF) sample at that time. The patient remained hospitalised for neurology rehabilitation and was recovering from pancreatitis. Six weeks after admission, the patient presented cervical, mandibular and inguinal adenopathy, with noticeable hepatosplenomegaly. CBC showed persistent pancytopenia. A new bone marrow aspirate showed severely altered architecture with fibrosis and blast clusters. A lumbar puncture presented blasts and the patient was diagnosed with a myeloproliferative disorder. Flow cytometry showed a B cell ALL, associated with CD66c and CD123 expression, negative response to prednisone, and hyperdiploidy (53–57 chromosomes). Chemotherapy with L-asparaginase and prednisone was started, without complications.

### DISCUSSION

Acute presentations of COVID-19 in paediatric patients are predominantly respiratory. These patients present with hypoxia, and complicated cases develop ARDS. Our patient had respiratory failure due to COVID-19, with mild heart failure, pancytopenia and increased inflammatory markers consistent with MIS-C. This combined presentation has been described in multiple populations, with higher mortality than other inflammatory presentations associated with SARS-CoV-2 infection in paediatric patients.<sup>6</sup> The patient had a quick and uncomplicated recovery of respiratory and haemodynamic failure. However, the pancytopenia was persistent and the differential of possible malignancy was suspected. This persistent pancytopenia has been described in other cases with ALL and COVID-19.<sup>7</sup> Persaud *et al*<sup>8</sup> described a paediatric patient with B cell ALL 1 week after a COVID-19 symptomatic infection. They explained this debut of leukaemia as leukaemogenesis triggered by a COVID-19 infection.<sup>8</sup> Leukaemogenesis in COVID-19 is yet to be defined by cohort studies, but our case is another example supporting this hypothesis. Haematological manifestations have different presentations in patients with COVID-19.<sup>9</sup>

Bone marrow studies are warranted in patients with persistent peripheral blood abnormalities. However, lymphodepletion associated with COVID-19 can make it difficult to reach a diagnosis even with a bone marrow sample. In addition, early initiation of therapies for COVID-19, including steroids, in critical care patients can result in inconclusive bone marrow studies. These treatments can delay the diagnosis of leukaemia in a bone marrow aspirate. According to a systematic review by Meena *et al*,<sup>2</sup> majority of patients with COVID-19 and malignancies were asymptomatic or with mild symptoms and later developed severe symptoms. These characteristics have been seen in cohorts of patients with COVID-19, including oncological patients, from different countries.<sup>10–13</sup>

The immediate complications that our patient had after the initial acute course were thought to be part of MIS-C features. Pancreatitis and encephalitis have been described as part of MIS-C. Imaging studies showed changes consistent with this diagnosis. However, these changes could also be associated with ALL, either primary leukaemia infiltrates or worsened by the SARS-CoV-2 infection.<sup>14</sup> The MRI spectroscopy study was thought to be helpful, directing the diagnosis to encephalitis. However, the spike in the tCho signal, seen in figure 3, is associated with increased membrane turnover (eg, in tumours, ischaemia, demyelination, inflammation and gliosis).<sup>15</sup> The broad diagnosis of MIS-C and the common inflammatory features with leukaemia made it difficult to obtain a final diagnosis. The timing of presentation of ALL in patients with COVID-19 has been described in other cases after 1 week of acute infection.<sup>8</sup> This timing coincides with the appearance of symptoms of MIS-C. This delay in diagnosis impacts the initiation of chemotherapy and can worsen outcomes.<sup>5 16</sup> Neurological complications during COVID-19 in paediatric patients have been associated with worst outcomes.<sup>17 18</sup> Appropriate management of these lesions regardless of aetiology must be recognised as these are critical complications that can have severe sequelae in patients with COVID-19. The number of patients with COVID-19 and malignancies with a complicated course is low. However, in paediatric patients with COVID-19 admitted to PICU, we should always suspect leukaemia and other cancers, particularly in patients presenting with inflammatory processes associated with SARS-CoV-2 and have a low index of suspicion.

### Learning points

- ▶ Paediatric patients with COVID-19 can have inflammatory diseases other than multisystemic inflammatory syndrome.
- ▶ New-onset malignancies have been associated with COVID-19 and should be suspected promptly in patients with atypical courses to avoid complications and delay in treatment.
- ▶ Neurological injuries occurring with COVID-19 are associated with increased morbidity and mortality.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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