Primary haemophagocytic lymphohistiocytosis (Chédiak-Higashi Syndrome) triggered by acute SARS-CoV-2 infection in a six-week-old infant

Haemophagocytic lymphohistiocytosis (HLH) is a rare haematologic disorder caused by dysregulation of the immune system, resulting in an overproduction of cytokines and an unrestrained haemophagocytosis. Primary (inherited) forms of HLH are linked to genetic mutations and have predominantly been described in the paediatric population. Secondary (acquired) forms of HLH may be triggered by infections or may develop in the context of autoimmune disease and malignancy. We present a case of primary HLH triggered by SARS-CoV-2 infection in a six-week-old infant, later diagnosed with Chédiak-Higashi syndrome (CHS).

Compared to adolescents and adults, infants and toddlers have mostly been mildly affected by the COVID-19 pandemic. The majority of infected infants and toddlers do not exhibit any symptoms.[1–3] Clinical signs of acute SARS-CoV-2 infection in a newborn may include high fever as well as respiratory and gastrointestinal symptoms. Haemodynamic or neurologic compromise is rare.[1,3] Nonetheless, some children develop a delayed hyperinflammatory syndrome. While adult COVID-19 patients may experience a cytokine storm, usually around day 7–10 of illness, paediatric multisystem inflammatory syndrome (MIS-C) typically presents 1–2 months following primary infection.[4] This MIS-C shares many clinical features with Kawasaki disease and is accompanied by markedly elevated inflammatory markers in serum.[5,6] While adults experience a critical pulmonary deterioration during an early cytokine storm, severe MIS-C presents mainly with cardiac or neurological involvement.

Following an uneventful pregnancy, the girl was born at full-term via vaginal delivery with an APGAR score of 9/9/10. She is the third child of consanguineous parents (first degree cousins). At six weeks of age she presented to a regional medical centre with acute onset of fever of up to 40°C and poor feeding. Following four days of symptomatic treatment, the patient was transferred to our institution. At our Paediatric Emergency Department, she showed tachypnoea of 70/min, an oxygen saturation of 85% (on room air), abdominal distension, and diarrhoea. Hepatosplenomegaly was documented by abdominal ultrasound, and chest x-ray revealed a pleural effusion without pulmonary infiltrates. The patient was admitted to the Peadiatric Intensive Care Unit, a nasopharyngeal PCR swab test was positive for SARS-CoV-2. The patient´s mother also tested positive by PCR. Laboratory testing showed severe anaemia, thrombocytopenia, elevated inflammatory markers, and deranged coagulation parameters. However, manual differentiation was unfortunately not carried out at that point in time. Clinical features and combined laboratory findings prompted the initiation of a specific diagnostic workup. Table I lists the pathological peripheral blood laboratory results. Plasma was PCR-negative for cytomegalovirus (CMV). Serology testing during the acute infection detected maternal antibodies against Epstein-Barr-virus (EBV) and varizella-zoster virus. Peripheral blood flow cytometry revealed lack of natural killer (NK) cell degranulation, and upon activation with anti-CD3/anti-CD28, lack of cytotoxic T-cell (CTL) degranulation. Perforin expression in NK cells and HLA-DR expression in $CD4^+$ – and $CD8^+$ T-lymphocytes were normal. A bone marrow aspirate showed CHS-characteristic inclusion bodies in band and segmented neutrophils. Scattered histiocytes and haemophagocytosis were detected. Genetic examination documented a known homozygous nonsense mutation in LYST (c5023G>T, p.Gly1675), confirming the diagnosis of CHS. Both parents

Table I. Laboratory results.

White blood cells	22·9 (6·5–15 10^3/µl)
Haemoglobin	**7·0 (9–17 mg/dl)**
Platelets	**25 (150–450 10^3/µl)**
Segmented neutrophils	**0·7 (2·5–11·0 10^3/µl)**
Monocytes	**0·9 (0·6–3·4 10^3/µl)**
Lymphocytes	3·9 (9·4–19·2 10^3/µl)
Unspecified cells	17·2 10^3/µl
T-lymphocytes	1·8 (2·3–3·11 10^3/µl)
NK cells	175 (200–1400/µl)
Quick/INR	<8/>5 (70–120%)
aPTT	117 (20–50 s)
D-Dimers	30 (<0·5 mg/l)
Antithrombin III	61 (70–120%)
Fibrinogen	**0·98 (2·55–3·75 g/l)**
Triglycerides	**4·77 (0·50–2·3 mmol/l)**
C-reactive protein	14 (<5 mg/l)
Ferritin	**4487 (10–200 ng/l)**
Soluble interleukin-2 receptor (sCD25) (Chemiluminescence Immunoassay-CLIA)	**16 899 (150–620 U/l)**
Lactate dehydrogenase	745 (130–370 U/l)

Pathological findings in bold.

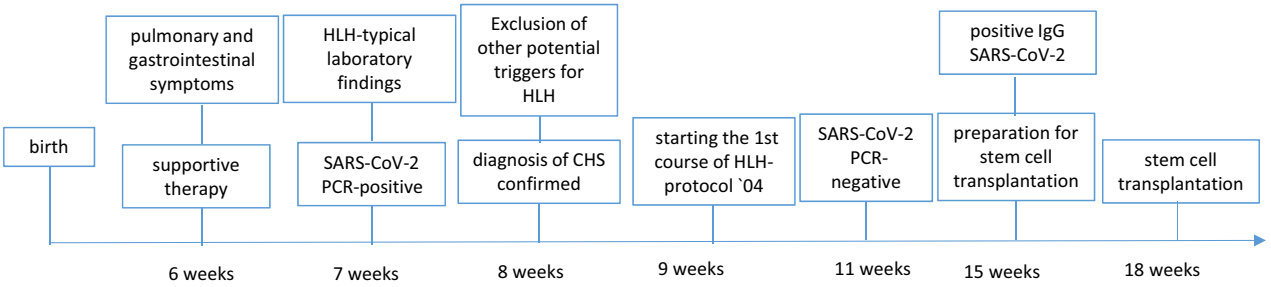

Fig 1. Timeline of symptoms and diagnostic procedures. [Colour figure can be viewed at wileyonlinelibrary.com]

were found to be heterozygous for the LYST mutation. Findings from light microscopy of scalp hair showed hypopigmentation consistent with the diagnosis.

Anaemia and thrombocytopenia required the transfusions of packed red blood cells and platelets. The patient received vitamin K and clotting factors. In accordance with the HLH-protocol 2004 treatment guidelines, the patient received dexamethasone, etoposide, and cyclosporine A. Over a course of two weeks, the patient's condition improved, and workup for stem cell transplantation was initiated. Serologic testing excluded hepatitis A, B, C, toxoplasmosis, syphilis, and herpes-simplex virus 1/2. Plasma was PCR-negative for hepatitis C, CMV, and West Nile virus. SARS-CoV-2 was undetectable by PCR-testing five weeks after the initial positive test results. SARS-CoV-2 Ig G serology turned positive after eight weeks. At four months of age, the patient underwent haematopoietic stem cell transplantation (HSCT) from a matched sibling donor. There has been no reactivation of SARS-CoV-2 during this time and the patient is alive and well. Figure 1 shows the timeline of clinical and diagnostic events, illustrating concurrent features of acute SARS-CoV-2 infection and HLH.

HLH is a hyperinflammatory syndrome with the hallmarks of unhinged T-cell proliferation, macrophage activation, and possibly defective NK cell degranulation in familial HLH.[7] Both primary (inherited) and secondary (acquired) forms of HLH may be triggered by various infectious agents. As such, neither the proof of an infection nor the patient's age at presentation sufficiently discriminates between primary and secondary forms of HLH.[7,8] EBV is known to be a particularly common trigger for both primary and secondary HLH.[8] There are some reports of SARS-CoV-2 triggering secondary HLH.[4–6] Until recently, SARS-CoV-2 had not been identified as a trigger for primary HLH. Alhumaidan *et al.* first reported the case of an infant who developed fatal HLH in the setting of an acute SARS-CoV-2 infection and was subsequently diagnosed with autosomal recessive familial HLH type 3.[9] Given the massive immune response elicited by SARS-CoV-2, it is conceivable that SARS-CoV-2 might be a potent trigger for primary HLH. Therefore, the diagnosis of primary HLH should be considered in children and adolescents presenting with signs of hyperinflammation in the setting of SARS-CoV-2 infection, especially early in the course of the disease, i.e., during the 'active' phase of infection and viral replication, and weeks before one might typically diagnose a MIS-C related cytokine storm. Our patient was PCR-positive for SARS-CoV-2 and was exhibiting typical symptoms of COVID-19. Simultaneously, laboratory findings were indicative of HLH. Taking into consideration clinical, pathological, and laboratory findings, the diagnosis of CHS was established and an appropriate therapy initiated. Notably, massive immunosuppression by HLH-2004, followed by conditioning, did not impair clinical recovery from SARS-CoV2 infection and viral clearance. We suggest including primary forms of HLH in the differential diagnosis of early hyperinflammatory states in young patients affected by SARS-CoV-2 infection.

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