Journal of Paediatrics and Child Health

doi:10.1111/jpc.16160

CASE REPORT

# Diagnostic challenges during the COVID-19 pandemic: A child with tuberculosis-induced haemophagocytic lymphohistiocytosis misdiagnosed as multi-inflammatory syndrome in children

Emel Celebi Congur,[1] Nazan Dalgic,[1] Halil I Ada,[2] Fazilet Türksoy[3] and Zeynep Y Yıldırmak[4]

Division of [1]Pediatric Infectious Diseases, [2]Radiology, [3]Pediatrics, and [4]Pediatric Hematology and Oncology, Sisli Hamidiye Etfal Training and Research Hospital, University of Health Sciences, Istanbul, Turkey

Haemophagocytic lymphohistiocytosis (HLH) is a hyper-inflammatory syndrome characterised by uncontrolled activation of macrophages, natural killer (NK) cells and cytotoxic T lymphocytes.[1] The disease is divided into two classes: primary (inherited) and secondary (acquired) HLH. Primary HLH is caused by genetic mutations, whereas secondary HLH can occur for various reasons, including infections, malignancies and autoimmune diseases.[2] Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe complication of coronavirus disease 2019 (COVID-19). In this article, we present a patient who was admitted to the intensive care unit (ICU) with a preliminary diagnosis of MIS-C but was later diagnosed with tuberculosis (TB)-induced HLH.

## Case Report

A 12-year-old Afghan boy was admitted to the hospital with fever and abdominal pain. Due to recent immigration of his family and lack of communication, it was not possible to obtain a detailed history. A thoracoabdominal computed tomography (CT) scan without contrast was performed, which showed minimal pleural effusion and free fluid in the abdomen. Ceftriaxone treatment was initiated because pneumonia and concomitant sepsis were suspected. After treatment was started, he was found to be COVID-19 IgG positive and had a ferritin level greater than 2000 μg/l. Based on the resistant fever, high inflammatory markers, and positive COVID-19 serology, a diagnosis of MIS-C was made. He was treated with intravenous immunoglobulin (IVIG). Because his fever persisted despite IVIG treatment, he was transferred to the paediatric intensive care unit (PICU). On admission to the PICU, oxygen saturation was 98% with the use of an oxygen mask, temperature was 38.5°C, heart rate was 130/min, and other vital signs were normal. The patient's height and weight were both below the 3rd percentile, while the other findings were normal. His medical history was unremarkable except for congenital hearing loss. The patient's 15-year-old brother also had hearing loss, his other siblings were healthy. Laboratory findings on admission are listed in Table 1. IVIG therapy was continued at a dose of 1 g/kg, and subcutaneous enoxaparin (2 × 0.5 mg/kg/dose) and methylprednisolone (2 mg/kg/day) were also administered. His fever decreased within 2 days and he was transferred to the ward on the fourth day. His echocardiography was normal. Methylprednisolone treatment was to be tapered and discontinued. During discontinuation, he had severe abdominal pain and fever on day 8, and serum, C-reactive protein (CRP) and procalcitonin levels were elevated (Table 1). As a result, ceftriaxone treatment was switched to piperacillin-tazobactam. An abdominal CT scan revealed liver and spleen enlargement and minimal pleural effusion in the right hemithorax. His blood count showed bicytopenia (Table 1), and he was referred to paediatric haematology, where a bone marrow aspiration was immediately performed. Multiple phagocytic macrophages were noted (Fig. 1), and a diagnosis of HLH was made. Viral serologies were negative, and immunoglobulin levels and lymphocyte subsets were all within the normal range. We decided to treat the patient with high-dose methylprednisolone (10 mg/kg/day). Before this treatment, a chest CT scan with contrast was performed to investigate a pleural effusion seen on his previous abdominal CT scan. The scan showed a peribronchovascular tree-in-bud pattern in both lungs (Fig. 2). This finding raised suspicion of non-specific bronchopneumonia, especially tuberculosis (TB), and corticosteroid treatment was postponed. On day 16, cultures were obtained from the fasting gastric aspirate and a paratracheal lymph node biopsy was performed. Acid-fast bacilli (AFB) were detected in the lymph node biopsy, and histology confirmed TB diagnosis. Anti-TB treatment

**Key points**

1. Haemophagocytic lymphohistiocytosis (HLH) is a hyper-inflammatory disease characterised by excessive and uncontrolled activation of the immune system. It can be triggered by infections.
2. HLH due to tuberculosis (TB) is an urgent situation that needs to be treated as soon as possible.
3. Multisystem inflammatory syndrome in children is a diagnosis of exclusion and may have very similar clinical findings to other severe diseases. A detailed history and physical examination are more valuable than laboratory tests in establishing a differential diagnosis.

**Correspondence:** Emel Celebi Congur, Division of Pediatric Infectious Diseases, Sisli Hamidiye Etfal Training and Research Hospital, University of Health Sciences, Kazım Karabekir Paşa Mah. Bahçeköy Cad. No: 64, 34453 Sarıyer/İstanbul, Turkey; email: emelcelebi@gmail.com

Grants: None.

Accepted for publication 26 July 2022.

**Table 1** Laboratory investigations during follow-up

| | Day 0 on admission to the PICU/at the time of the first attack | Day 4 on transfer to the infectious diseases ward | Day 8 at the time of his second febrile attack | Day 16 after starting anti-TB drug treatment + high dose steroid | Day 27 at the time of the third febrile attack, when the HLH-2004 protocol started | Day 64 on discharge |
|---|---|---|---|---|---|---|
| Haemoglobin (g/L) | 7.5 | 7.3 | 6.7 | 9.6 | 11.1 | 9.4 |
| Leukocyte ($10^9$/L) | 4.2 | 2.4 | 8.6 | 6.9 | 6.2 | 4.5 |
| Neutrophil ($10^9$/L) | 2.88 | 1.61 | 7.58 | 5.74 | 4.4 | 3.0 |
| Lymphocyte ($10^9$/L) | 1.15 | 0.7 | 0.78 | 0.8 | 1.3 | 0.9 |
| Platelets ($10^9$/L) | 326 | 431 | 125 | 225 | 381 | 321 |
| CRP (mg/L) (reference: <5) | 24.8 | 15.5 | 107 | 53.1 | 30.9 | 21 |
| Procalcitonin (μg/L) (reference: <0.5) | 5.8 | 1.6 | 5.46 | 0.76 | 0.5 | 0.06 |
| Ferritin (μg/L) (reference: <360) | 2891 | 3174 | 1408 | 906 | 719 | 151 |
| Fibrinogen (g/L) (reference: 2.5–4.5) | 5.12 | 4.27 | 5.45 | 5.05 | 3.6 | – |
| D-dimer (μg/L) (reference: <500) | 1697 | 2951 | 2229 | 3478 | 1915 | – |
| Triglyceride (mg/dL) (reference: <130) | – | – | 78 | 54 | 75 | 56 |

CRP, C-reactive protein; HLH, haemophagocytic lymphohistiocytosis; PICU, pediatric intensive care unit.

(isoniazid-rifampicin-ethambutol-pyrazinamide) and methylprednisolone (10 mg/kg/day for 3 days) were started simultaneously. The fever and acute phase reactants resolved immediately after the start of treatment. However, fever recurred on day 27 after discontinuation of steroid treatment. Therefore, the methylprednisolone dose was increased again to 10 mg/kg/day, and he received anakinra and IVIG. During the discontinuation of methylprednisolone therapy, he had high fever for the third time, and blood tests indicated a new episode of haemophagocytosis. On day 32, a second bone marrow aspiration revealed numerous haemophagocytic macrophages. Based on these findings, the HLH-2004 protocol (cyclosporine+etoposide+dexamethasone) was initiated.[2] In the meantime, drug-susceptible *Mycobacterium tuberculosis* was grown from the gastric aspirate. Genetic testing was performed for familial haemophagocytosis. The UNC13D, STX11 and PRF1 genes were found to be normal. Fever did not recur after initiation of the HLH-2004 protocol. The patient was discharged home in good

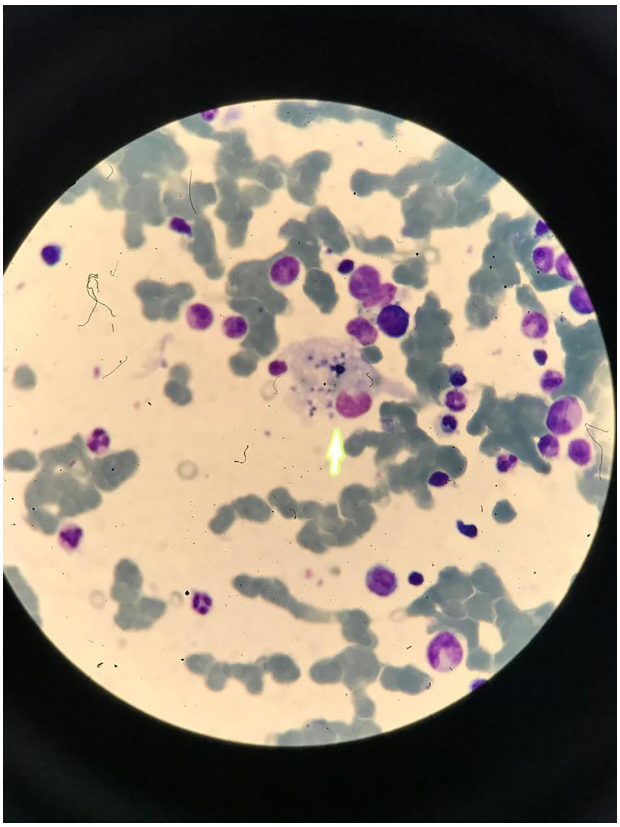

**Fig. 1** Bone marrow smear stained with May-Grünwald-Giemsa stain showing haemophagocytosis.

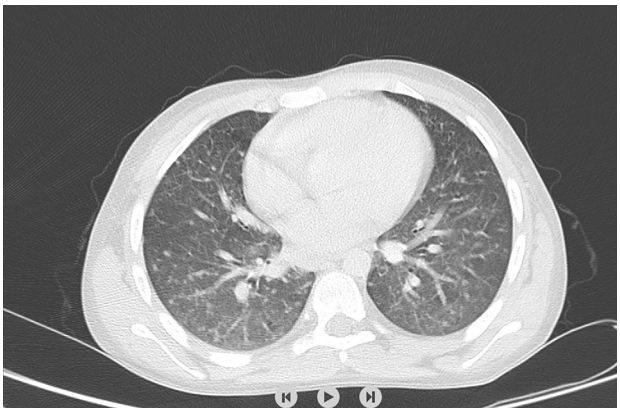

**Fig. 2** Thorax CT: peribronchovascular tree in bud pattern in both lungs, endobronchial spread – interpreted as likely tuberculosis. CT, computed tomography.

**Table 2** Diagnostic guidelines for haemophagocytic lymphohistiocytosis (HLH)

| |
|---|
| 1 A molecular diagnosis consistent with HLH (e.g., pathologic mutations of the primary HLH genes) |
| OR |
| 2 Five out of the eight criteria listed below are met |
| i Fever ≥ 38.5°C |
| ii Splenomegaly |
| iii Cytopenias (affecting at least two lineages in the blood): haemoglobin < 9 g/dL, platelets < 100 000/mL, neutrophils < 1000/mL |
| iv Hypertriglyceridaemia (fasting > 265 mg/dL) and/or hypofibrinogenaemia (<150 mg/dL) |
| v Haemophagocytosis in bone marrow or spleen or lymph nodes or liver without evidence of malignancy |
| vi Low or absent natural killer (NK) cell activity |
| vii Ferritin higher than 500 ng/mL |
| 3 Elevated soluble CD25 (alpha chain of soluble IL-2 receptor) |

*Table is adapted from Lanzkowsky's Manual of Paediatric Haematology and Oncology, Seventh Edition.

condition. Today, he continues to be followed for TB treatment in our outpatient clinic.

The patient's family provided written informed consent for this case report.

## Discussion

HLH is a devastating hyperinflammatory disease caused by uncontrolled macrophage and lymphocyte activation. Both primary and secondary HLH can occur at any age.[1] Familial HLH is caused by mutations in the PRF1, UNC13D, STX11 and STXBP2 genes, which affect the lymphocyte-perforin pathway. In our patient, mutations in PRF1, UNC13D and STX11 genes were investigated, which are the most common in the Turkish population.[3] Secondary HLH is triggered by underlying diseases such as infections, malignancies and inflammatory diseases.[4] HLH is often associated with viral infections, including EBV, CMV, parvovirus, HSV, VZV, HHV-8, influenza and HIV. Less commonly, bacterial (including tuberculosis), parasitic and fungal infections can also lead to this clinical picture.[5]

During the COVID-19 pandemic, it is difficult to distinguish between HLH and MIS-C, as both share similar pathophysiology and clinical findings. TB is known as the 'great mimicker' because its clinical manifestations are enormously diverse and it is frequently misdiagnosed.[6] Our patient was misdiagnosed as MIS-C on initial admission because his symptoms were non-specific and his SARS-CoV-2 IgG was positive. We want to point out that since the pandemic has been ongoing for more than 2 years, COVID-19 serology is usually positive, so laboratory findings are not superior to history and physical examination. Unfortunately, a detailed history could not be obtained from his mother, who is also an Afghan refugee, which would have been crucial for a correct diagnosis.

The diagnosis of HLH is made using the diagnostic criteria published in the 2004 HLH guideline (Table 2).[2,7] However, we could not perform elevated soluble CD25 and NK cell activity because of the lack of insurance. Resistant fever that did not respond to broad-spectrum antibiotics, bicytopenia, splenomegaly and high ferritin levels led us to suspect haemophagocytosis. As a result, a paediatric haematologist was consulted, a bone marrow aspiration was performed, and numerous phagocytic macrophages were detected. Ultimately, he met five of the eight criteria in the 2004 HLH guideline and was diagnosed with HLH. Initial methylprednisolone treatment masked the clinical findings and therefore delayed the actual diagnosis.

Among secondary causes of HLH, TB is reported to constitute 3%.[8] If anti-TB treatment is not initiated for TB-associated HLH, mortality is close to 100%. This mortality can be reduced by 40–60% with concurrent anti-TB treatment and immunotherapy.[6] The cornerstone of treatment is initiation of effective anti-TB treatment in the early phase. In our patient, a transient clinical response to steroid and IVIG treatment was initially observed, but resistant fever recurred during tapering. After starting anti-TB treatment with the HLH-2004 protocol, his clinical condition improved dramatically despite the delay in diagnosis.

HLH due to TB is an urgent situation that needs to be diagnosed and treated as soon as possible. For the past 2 years, clinicians have been very focused on COVID-19 and MIS-C. Although we are alarmed about COVID-19 and related diseases because of the pandemic, we should also keep other infectious diseases in mind during differential diagnosis. We should always remember that MIS-C is a diagnosis of exclusion.

## Conflict of interest

The authors declare no conflicts of interest.

## References

1 Al-Samkari H, Berliner N. Hemophagocytic lymphohistiocytosis. *Annu. Rev. Pathol.* 2018; **13**: 27–49.
2 Henter JI, Horne A, Aricó M *et al*. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr. Blood Cancer* 2007; **48**: 124–31.
3 Ahmari AA, Alsmadi O, Sheereen A *et al*. Genetic and clinical characteristics of pediatric patients with familial hemophagocytic lymphohistiocytosis. *Blood Res.* 2021; **56**: 86–101.
4 Bergsten E, Horne A, Aricó M *et al*. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: Long-term results of the cooperative HLH-2004 study. *Blood* 2017; **130**: 2728–38.
5 Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome [published correction appears in Lancet. 2014 Apr 26;383(9927):1464]. *Lancet* 2014; **383**: 1503–16.
6 Zhang Y, Liang G, Qin H, Li Y, Zeng X. Tuberculosis-associated hemophagocytic lymphohistiocytosis with initial presentation of fever of unknown origin in a general hospital: An analysis of 8 clinical cases. *Medicine* 2017; **96**: e6575.
7 Eckstein OS, Allen CE. Hemophagocytic lymphohistiocytosis. In: Fish JD, Lipton JM, Lanzkowsky P, eds. *Lanzkowsky's Manual of Pediatric Hematology and Oncology*, 7th edn. London: Academic Press; 2022; 371–6.
8 Shea YF, Chan JF, Kwok WC *et al*. Haemophagocytic lymphohistiocytosis: An uncommon clinical presentation of tuberculosis. *Hong Kong Med. J.* 2012; **18**: e517–25.