Haemophagocytic lymphohistiocytosis in an adult with postacute COVID-19 syndrome

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SUMMARY

Haemophagocytic lymphohistiocytosis (HLH) causing multiorgan failure has been reported as an acute clinical presentation of COVID-19. However, the literature surrounding HLH in the context of a postacute COVID-19 syndrome is limited. This report presents a case of a life-threatening HLH occurring 6 weeks after a pauci-symptomatic COVID-19 infection in a previously healthy adult. A bone marrow aspirate confirmed the HLH and the patient was successfully treated with dexamethasone and etoposide. To our knowledge, this is the first case of HLH occurring as a postacute COVID-19 syndrome following a pauci-symptomatic initial infection.

BACKGROUND

According to the WHO, there are currently over 164 million confirmed cases of COVID-19 worldwide, including over 3 million deaths.[1] Macrophage activation, and more specifically haemophagocytic lymphohistiocytosis (HLH), is one among many acute clinical presentations of COVID-19 and is a medical emergency with a poor prognosis.[2]

Recently, Nalbandian *et al*[3] defined postacute COVID-19 syndrome as persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms. As it stands, the severity of the initial COVID-19 illness is considered a risk factor for developing postacute COVID-19 syndrome. Despite the elaborate list of possible manifestations of the postacute COVID-19 syndrome, HLH is not mentioned.[3] This report presents the first case of a life-threatening HLH occurring 6 weeks after a pauci-symptomatic COVID-19 infection, and therefore suggests that HLH can manifest as a postacute COVID-19 syndrome.

CASE PRESENTATION

A 54-year-old multiracial man originally from the Dominican Republic presented with a 2-day history of fever, acute right-sided anterior neck pain and neck swelling. His medical history was limited to a prior episode of uncomplicated sigmoid diverticulitis.

Six weeks prior to the current emergency room (ER) visit, the patient was diagnosed with COVID-19, confirmed by PCR via nasopharyngeal swab. At the time, he experienced fever and chest tightness. As the patient did not feel overly encumbered by his illness, he simply self-isolated and his symptoms resolved within 1 week without treatment. No physical examination or laboratory testing was performed. According to the patient, he was not re-exposed to COVID-19 prior to his current ER visit; he was, however, in public areas.

At the current presentation, a CT scan of the neck revealed multiple, enlarged, right cervical lymph nodes with surrounding fat stranding. A presumed diagnosis of cervical lymphadenitis was made, resulting in hospital admission and treatment with intravenous piperacillin-tazobactam (4.5 g every 8 hours). Four days after the admission, his fever persisted and he developed new erythema at the right cervical region prompting a change of treatment to meropenem (1 g every 8 hours) and intravenous vancomycin (750 mg every 12 hours) for suspected cellulitis. The following day, the patient remained febrile and developed tachycardia, hypoxia and abdominal pain (figure 1). He was transferred to the intensive care unit (ICU) with a presumed diagnosis of bacterial sepsis from a cervical skin infection.

On day 6, the patient's condition quickly deteriorated to a multiorgan failure with significant respiratory distress, hypotension, acute kidney injury, and elevated transaminases and troponin. He was intubated and treated with vasopressors and continuous renal replacement therapy (CRRT).

INVESTIGATIONS

On arrival to the ICU, the patient had two documented negative PCR COVID-19 tests (he eventually had four more while in the ICU, all of which were negative).

A full body CT scan on day 5 revealed stable right-sided cervical lymphadenopathy, with new extension of inflammation into the subcutaneous tissues along the lateral neck, new fluid in the right retropharyngeal space, prominent mediastinal lymph nodes, peribronchovascular confluent opacities and interlobular septal thickening with bilateral pleural effusions, as well as pancolitis with a small amount of ascites (figure 2).

Laboratory values from the day 6 decompensation revealed the following: haemoglobin of 94 g/L, platelets of 383×10^9, neutrophils of 34.9×10^9, lymphocytes of 1.08×10^9, monocytes of 1.93×10^9, C reactive protein of 3.84×10^2 mg/L and a ferritin level of 1.02×10^5 μg/L (table 1).

On the same day, the patient underwent open exploration of his right neck, which revealed no necrotic tissue nor pus. A cervical lymph node biopsy revealed a reactive lymph node without any evidence of tumour or granulomas. All microbial stains and cultures performed on the neck tissues were negative. An extensive infectious work-up (table 2) yielded negative results. An autoimmune work-up was negative as well.

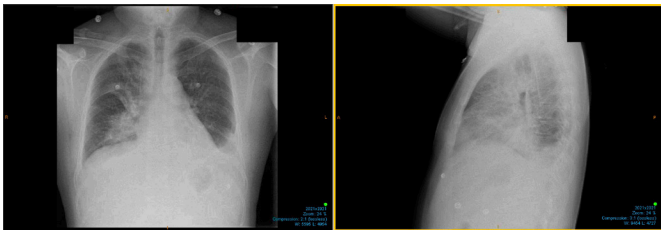

Figure 1 Chest X-ray from day 4 demonstrating bilateral small pleural effusions, diffuse bilateral reticular densities, and right upper lobe and lower consolidations.

A transthoracic echocardiogram (TTE) a day later revealed diffuse hypokinesis of the left ventricle with severe systolic dysfunction and an ejection fraction of 20%. A repeat ferritin was $8.40\times10^4\,\mu$g/L, triglycerides were 2.28 mmol/L, lactate dehydrogenase was 6.32×10^3 U/L and plasma interleukin 6 (IL-6) was 3.15×10^2 ng/L.

A suspicion for HLH led to a bone marrow aspirate which revealed haemophagocytosis (figure 3). No evidence of lymphoma or cytomegalovirus (CMV) intranuclear inclusions was seen; bacterial, mycobacterial and fungal cultures performed on the bone marrow aspirate showed no growth.

DIFFERENTIAL DIAGNOSIS

Given the combination of multiorgan failure, systemic inflammation and elevated cytokines, the patient seemed to be suffering from a cytokine storm. There exists, however, significant overlap in the diseases that constitute the cytokine storm spectrum. The differential diagnoses included bacterial sepsis, toxic shock syndrome, viral infection, autoinflammatory disorder (such as systemic lupus erythematosus, vasculitis), multicentric Castleman disease and other human herpes virus-8-related conditions, secondary HLH, and multisystem inflammatory syndrome associated with SARS-CoV-2.

At the time of decompensation, the patient met three of eight HLH 2004 criteria with a calculated HScore of 162, indicating a 40%–54% probability of a haemophagocytic syndrome.[4 5]

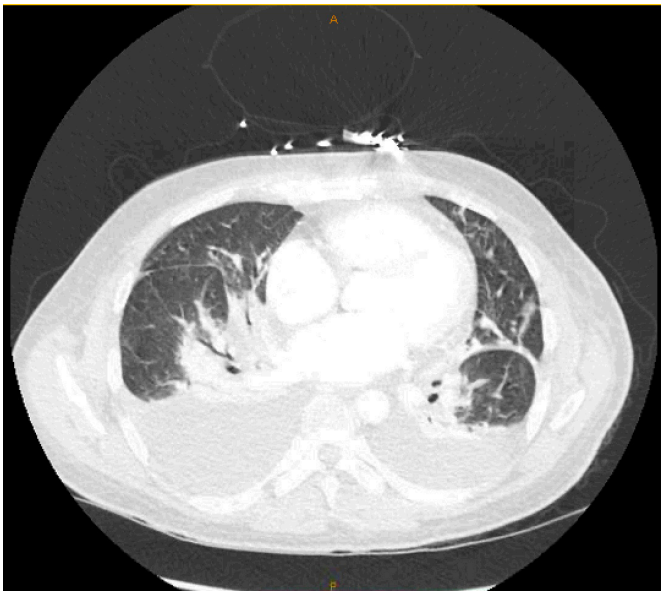

Figure 2 CT angiogram of the chest from day 5 demonstrating peribronchovascular confluent opacities and interlobular septal thickening, bilateral pleural effusions and mild anasarca.

Table 1 Laboratory results from days 0, 6, 15 and 28

Laboratory test	Day 0 (in the emergency room)	Day 6	Day 15	Day 28
Haemoglobin (g/L)	137	94	75	73
Platelets ($\times10^9$/L)	174	383	267	229
White cell count ($\times10^9$/L)	18.0	38.0	28.4	4.20
Absolute neutrophils ($\times10^9$/L)	15.8	34.9	27.9	3.61
Absolute lymphocytes ($\times10^9$/L)	0.82	1.08	0.20	0.27
Absolute monocytes ($\times10^9$/L)	1.25	1.93	0.14	0.16
Creatinine (µmol/L)	71	193	313	361
Alanine aminotransferase (U/L)	36	2.07×10^3	62	24
C reactive protein (mg/L)	310	364	124	173
Ferritin (µg/L)	Not done	1.02×10^5	952	291
Triglycerides (mmol/L)	Not done	2.28	1.60	1.23
Lactate dehydrogenase (U/L)	174	6.32×10^3	Not done	263
Interleukin 6 (ng/L)	Not done	315	Not done	Not done

The addition of the bone marrow aspirate showing haemophagocytosis increased the patient's HScore to 197 for an 80%–88% probability. Notably, the absence of acute Epstein-Barr virus (EBV), CMV and HIV infections and the unremarkable autoimmune panel also contributed to the diagnosis.

TREATMENT

Given the suspicion of HLH, the patient was treated with a pulse dose of 1000 mg of methylprednisolone pending the bone marrow aspirate result. The ferritin decreased to $7.63\times10^3\,\mu$g/L after 3 days of methylprednisolone.

On day 12 in hospital, the patient received a first dose of etoposide (175 mg) and started daily dexamethasone (18 mg) for 2 weeks.

On day 15, now haemodynamically stable, a repeat TTE showed an improvement of the left ventricular systolic function with an ejection fraction of 50%; therefore, only dexamethasone was continued and the patient was extubated. On day 16, however, the patient was again breathless, febrile and confused; ferritin reincreased to $1.73\times10^3\,\mu$g/L (from $7.77\times10^2\,\mu$g/L). He was reintubated and vasopressors and CRRT were restarted. Once a septic work-up confirmed the absence of a new infection, he received another dose of etoposide on day 21. The following day, he was afebrile and no longer required vasopressor support.

On day 28 in hospital, the patient received a third dose of etoposide, and dexamethasone had already been decreased (9 mg intravenously). His ferritin normalised to $2.91\times10^2\,\mu$g/L, as did the triglycerides to 1.56 mmol/L and the lactate dehydrogenase to 1.86×10^2 U/L (table 2).

OUTCOME AND FOLLOW-UP

Unfortunately, soon after, the patient developed bronchopleural fistula requiring lung-protective ventilation; this was thought to have been caused by barotrauma in the context of a COVID-19-related parenchymal lung injury. A repeat CT of the chest showed no evidence of fibrosis (figure 4). The fistula was managed by adopting a lung-protective ventilation strategy.

Next, as a consequence of adopting a lung-protective ventilation strategy, the patient developed hypercapnic respiratory failure. Due to significant hypercapnia and also due to difficulty oxygenating in the context of worsening adult respiratory distress syndrome (ARDS) from HLH combined with a lung-protective ventilation strategy, venovenous extracorporeal membrane

Table 2 Infectious and autoimmune work-up performed between days 6 and 8

Aerobic and anaerobic blood cultures (–) ×2	Antinuclear Ab (–) at a titre of 1:160
Urine culture (–)	Antiextractable nuclear Ab not done
BAL culture (–), *Mycoplasma pneumoniae* BAL (–), *Legionella* BAL (–), PJP BAL (–), hantavirus BAL (–), aspergillus antigen BAL 0.09, galactomannan BAL (–)	Anti-DNA Ab not done
SARS-CoV-2 NAAT on BAL (–), Biofire V.2.1 plus multiplex-22 respiratory infections performed on BAL (–), TB sputum culture (–)	Rheumatoid factor quantitative <10 IU/mL
HIV Ab/Ag screen (–)	Anti-MPO <2 RU/mL, anti-PR3 <2 RU/mL
Hepatitis B sAg (–), hepatitis B sAb=0.0 IU/L, hepatitis B cAb (–), hepatitis C Ab (–)	Lupus anticoagulant dRVVT screen 63.5 s, dRVVT confirm 1.37 ratio, PTT-LA 61.7 s
Toxoplasma IgM=0.19 s/co, IgG 19.4 IU/mL	B2 glycoprotein 4.90 U/mL
CMV quantitative by PCR not detected	Anticardiolipin IgM <2, IgG <2
EBV VCA IgM (–), VCA IgG (+), EBNA IgG (+), EBV PCR quantitative 661 copies/mL	
Bartonella henselae IgG=1:160	
Enterovirus PCR blood (–), adenovirus PCR blood (–)	
HTLV-I/II screen ELISA (–)	
Coccidioides Ag in urine (–)	
Histoplasma capsulatum Ag ELISA (–), IgM (–), IgG (–)	
Strongyloides OD=0.12, *Strongyloides stercoralis* NIE (–)	
Neck tissue bacterial culture (–), neck tissue AFB culture (–), pleural fluid culture (–)	

Ab, antibody; AFB, acid-fast bacteria; Ag, antigen; BAL, bronchoalveolar lavage; cAb, core antibody; CMV, cytomegalovirus; dRVVT, dilute Russell's viper venom time; EBNA, Epstein-Barr nuclear antigen; EBV, Epstein-Barr virus; HTLV, human T cell lymphotropic virus; IU, international units; MPO, myeloperoxidase; NAAT, nucleic acid amplification test; NIE, recombinant antigen; OD, optical density; PJP, *Pneumocystis jirovecii*; PR3, proteinase 3; PTTLA, partial thromboplastin time lupus anticoagulant; RU, relative units; sAb, surface antibody; sAg, surface antigen; s/co, signal-to-cut-off; TB, tuberculosis; VCA, viral capsid antigen.

oxygenation (ECMO) was initiated on day 31 (figure 5). On day 41, the patient underwent percutaneous tracheotomy (figure 6). On day 64, ECMO support was stopped as both oxygenation and ventilation were adequately performed by a ventilator.

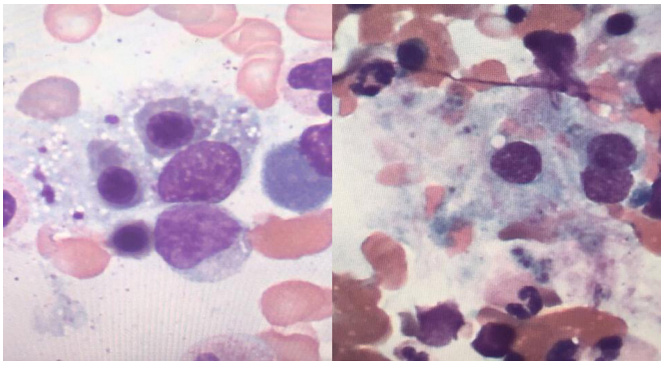

Figure 3 Bone marrow aspirate showing haemophagocytosis.

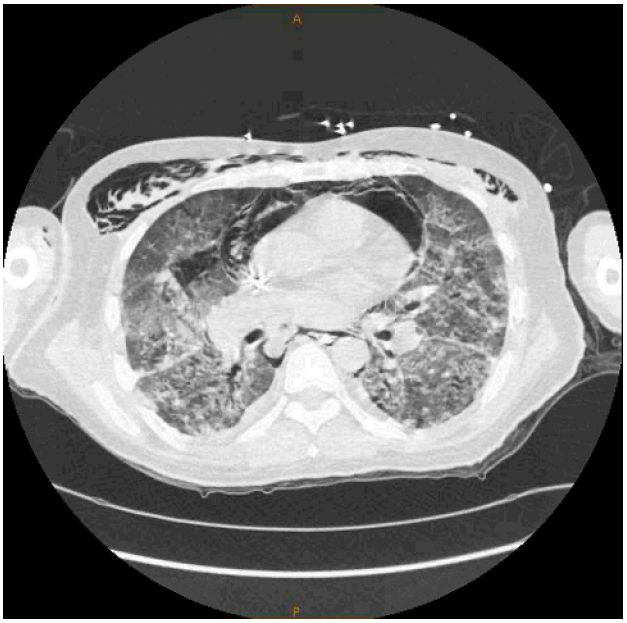

Figure 4 CT of the chest from day 24 demonstrating interval development of a significant pneumomediastinum, interstitial emphysema in the right middle lobe and bilateral subcutaneous emphysema, and diffuse peribronchovascular mixed attenuation nodular opacities.

At the time of this report, the patient is hospitalised in a ventilatory weaning unit where he is neurologically and haemodynamically stable.

DISCUSSION

Since its discovery in 1939, at which point it was known as histiocytic medullary reticulosis, HLH has proven to be a perplexing condition.[6] Conventionally, HLH is grouped into two distinct categories: primary and secondary. Primary occurs

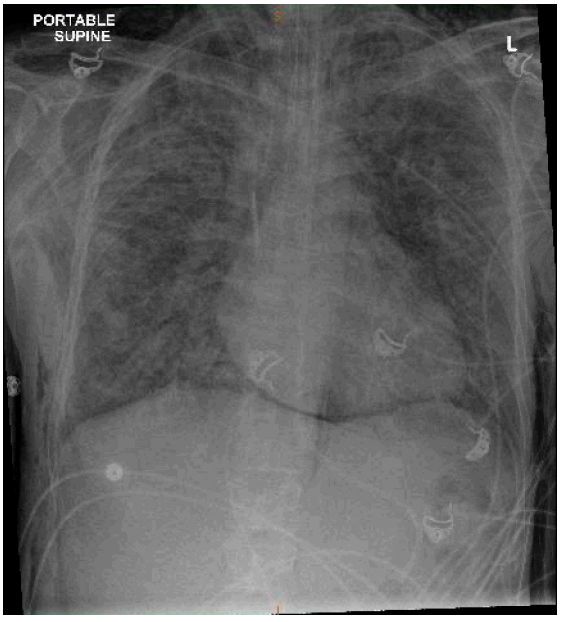

Figure 5 Chest X-ray from day 30 demonstrating known pneumomediastinum, persistent thoracic subcutaneous emphysema, interval progression of diffuse airspace and consolidated opacities.

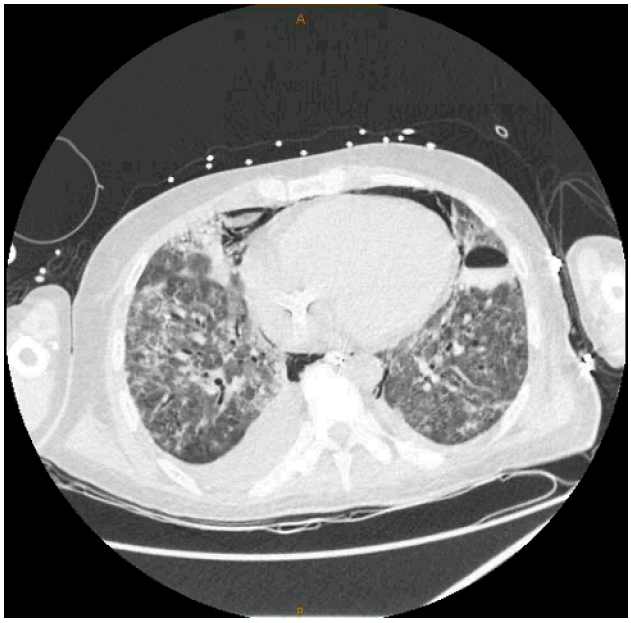

Figure 6 CT of the chest from day 43 demonstrating extensive pneumomediastinum and subcutaneous emphysema, new loculated fluid along the left major fissure with a hyperdense component, small bilateral uncomplicated pleural effusions, and bilateral diffuse parenchymal consolidations.

more often in children, in the setting of a genetic predisposition, which disrupts cytotoxic T cell and inflammasome functions. Secondary occurs more often in adults, in the absence of a genetic predisposition, but in the context of an immunological trigger (infection, malignancy, etc).[7] Both forms are engendered by a dramatic activation of cytotoxic T cells and natural killer cells combined with macrophage activation. Such an uncontrolled immune activation syndrome can lead to a cytokine storm, which can be life-threatening.[6]

The incidence of HLH in adults is low, ranging from 1 in 2000 patients admitted to tertiary care centres to 1 in 800 000 seen in a Japanese nationwide survey.[8 9] The mean age in adults is reported to be around 50 years, and approximately two-thirds of cases occur in men; it remains unclear whether certain races and ethnic groups are predisposed to developing HLH.[6] Current guidelines recommend using the HLH 2004 criteria for diagnosis in adults; however, this recommendation is based on expert opinion, as these criteria have only been validated in children. The HScore, developed by Fardet *et al*, represents another diagnostic tool.[5] Finally, flow cytometry of CD38 and human leukocyte antigen DR type (HLA-DR) expression on $CD8^+$ T cells has recently been proposed as another diagnostic aid.[10]

With regard to treatment, the abovementioned guidelines recommend regimens that include etoposide with the target of controlling hyperinflammation; the intensity and duration of treatment are therefore variable.[11]

Several studies have illustrated a close relationship between HLH and viral infections, most commonly, EBV, HIV and CMV.[12] Interestingly, SARS-CoV-2 has also been reported to lead to secondary HLH.[2] Unfortunately, the mortality rate of COVID-19-induced HLH is reported to be as high as 54%.[13]

The patient described in this case report meets the criteria for a postacute COVID-19 syndrome as he had a documented infection 6 weeks prior and his repeat COVID-19 PCR tests during this admission (six in total) were all negative. What is striking, however, is that this patient suffered from a pauci-symptomatic COVID-19 illness as he did not require treatment nor hospitalisation and his symptoms self-resolved within 1 week, yet he developed HLH, a life-threatening immune reaction.

As mentioned in the differential diagnosis, when the patient arrived to the ICU, a multisystem inflammatory syndrome was proposed as a possible diagnosis. Notably, multisystem inflammatory syndrome in children is listed as a possible postacute COVID-19 syndrome, yet the adult form is not.[3] Nevertheless, increasing literature is emerging surrounding the adult entity. The centre for disease control (CDC) defines multisystem inflammatory syndrome in adults (MIS-A) as patients who, in the absence of an alternative diagnosis, are aged over 21 years, are severely ill, currently have a positive SARS-CoV-2 test or have had a positive test in the last 12 weeks, have evidence of organ dysfunction in at least two extrapulmonary sites, do not have a severe respiratory illness, and who exhibit laboratory evidence of severe inflammation.[14] At this time, whether haemophagocytosis is a feature of MIS-A remains unknown. In this case, it was felt that HLH was a reasonable alternative diagnosis.

Of note, the patient developed a significant but transient worsening in his cardiac function. This was thought to be a stress (or Takotsubo) cardiomyopathy induced by the HLH. Stress cardiomyopathy occurs when there is transient systolic dysfunction that is associated with a physical or emotional stress. With resolution of the underlying stressor, cardiac function is generally restored within 1–4 weeks, which is what occurred in this case.[15]

It remains unclear why very few patients develop HLH after SARS-CoV-2 infection. It is hypothesised that an aberrant virus–host interaction occurs in the context of elevated cytokines, including IL-6 levels. IL-6 is a major driver of B cell hyperfunction leading to polyclonal expansion. Excessive release of IL-6 has been linked to numerous autoimmune diseases.[16] Of note, tocilizumab, an anti-IL-6 receptor monoclonal antibody, was not administered in this case of postacute COVID-19 syndrome since it was thought that tocilizumab would not have blocked the phagocytosis process at the origin of the HLH.

Naous *et al*[17] described a 69-year-old woman who presented with HLH documented by a bone marrow aspiration 3 weeks after her COVID-19 infection. In contrast to this case, the patient presented within 4 weeks of her initial infection and she required hospitalisation as well as intravenous steroids during her initial infection. Despite treatment with dexamethasone and etoposide, the patient did not survive.[17]

The presented case of HLH following a pauci-symptomatic COVID-19 infection illustrates a delayed and severely modified immune response against SARS-CoV-2 and represents a

Learning points

- COVID-19-associated haemophagocytic lymphohistiocytosis (HLH) can present as a postacute COVID-19 syndrome, even after a pauci-symptomatic initial infection.
- The development of HLH after a SARS-CoV-2 infection is rare and represents an aberrant virus–host interaction.
- HLH remains a diagnostic challenge since it can mimic severe infections, autoimmune diseases, lymphoproliferative disorders and multisystem inflammatory syndrome in adults.
- A bone marrow aspirate and/or biopsy should be performed on speculation to help facilitate an early diagnosis.
- The optimal duration of immunosuppressive therapy should be made on a case-by-case basis due to the elevated risk of bone marrow suppression and infection.

new entity on the list of postacute COVID-19 manifestations. A high index of suspicion is necessary for the diagnosis of HLH in patients who have recovered from COVID-19. Bone marrow aspiration and/or biopsy should be carried out promptly to confirm the diagnosis and start appropriate treatment for HLH.

There is currently no guidelines or algorithm for optimal follow-up of patients who have recovered from COVID-19. Nevertheless, several institutions have already created post-COVID-19 recovery clinics. A follow-up visit (or telemedicine visit) weeks to months after the initial infection, regardless of the severity, might help both to ensure resolution of the prior symptoms and assess for emerging postacute COVID-19 manifestations.

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