



# Cytomegalovirus pneumonitis-induced secondary hemophagocytic lymphohistiocytosis and SIADH in an immunocompetent elderly male literature review



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## ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is also known as hemophagocytic syndrome. It is a lethal hematologic condition due to a dysregulated immune response which results in inappropriately activated macrophages damaging host tissues. Based on the etiology, HLH can be primary (genetic) or secondary (acquired). The most common cause of a secondary HLH is an infection. Viral infections are the most common cause of secondary HLH. Among the viral causes of secondary HLH, Epstein–Barr virus is the most common etiologic agent. Cytomegalovirus (CMV) is a common causative pathogen in the immunocompromised host but is rare in an immunocompetent adult. In infection-associated secondary HLH, treatment includes antimicrobial therapy. HLH carries a high mortality and morbidity rate as it is an underdiagnosed clinical condition. Successful early diagnosis allows for adequate time for curative therapy. Treatment for HLH includes chemotherapy, immunomodulators, and a hematopoietic stem-cell transplant. The 2004 diagnostic criteria set by the Histiocyte Society serves as a guide to make an earlier clinical diagnosis. A review of PubMed literature revealed only five reported cases of CMV-induced HLH. We describe the sixth case of CMV pneumonitis-induced HLH and syndrome of inappropriate antidiuretic hormone secretion in a 72-year-old White male. He was treated successfully with oral valganciclovir and corticosteroids.

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## Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a rare critical illness resulting from disorganized immune activation of macrophages and defective cytotoxic cell function resulting in a cytokine storm detrimental to the host tissues. Without treatment, the damage to hematopoietic cells results in profound neutropenia and T lymphocyte cell immunosuppression. Finally, death ensues from a bacterial or fungal infection. An infection can trigger both primary and secondary HLH. Primary HLH results from a genetic flaw associated with fixed defects in cytotoxic cell function, which frequently presents in infancy and rarely in the seventh decade of life. Secondary HLH occurs due to infection, malignancies, autoimmune diseases, and immunosuppression

with a presentation later in older children and adults. Infections account for the most common cause of secondary HLH [1]. Epstein–Barr virus (EBV) infection is the most common infection responsible for HLH in healthy individuals [1]. Cytomegalovirus (CMV)-associated HLH is common in immunodeficient states such as autoimmune disease, infection, and solid organ transplantation. In secondary HLH, treatment of the underlying cause controls the unchecked inflammatory cascade and, ultimately, its end [2]. Upon review of PubMed, only five other case reports describe CMV-associated HLH in immunocompetent patients (Table 1). Without treatment, secondary HLH carries a high mortality and morbidity, with most patients dying in less than two months [1]. HLH 2004 diagnostic criteria (Table 2) enable an earlier detection to avoid the prolonged delay in diagnosis and treatment with a decrease in mortality by 30–35% [3]. In this case report, we describe a healthy White elderly male who presented with high-grade fever, worsening dyspnea, and dry cough. Ultimately he was diagnosed with secondary HLH due to acute CMV pneumonitis.

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**Table 1**  
Patient's characteristics in priorly reported CMV-associated HLH in immunocompetent patients.

Reference	Tsuda and Shirono. (1996)	Hot et al. (2008)	Yu-TzuTseng et al. (2011)	Atim-Oluk M. (2013)	Bonnecaze AK. (2017)
Age/gender	21/male	32/female	No details	48/female	39/female
Medical history	None	None	No details	Irritable bowel syndrome Benign leiomyoma	Diabetes mellitus HTN OSA
Site of involvement	Cervical Lymphadenopathy	Skin rash Haematological Transaminitis Splenomegaly	No details	Dyspnea, lethargy, Abdominal pain, CMV colitis & pneumonitis	Night sweats, Fever, Abdominal pain, CMV pneumonitis
Diagnostic criteria for CMV	CMV IgG and CMV IgM positive	CMV visualized within leucocytes. CMV IgM + Low avidity CMV IgG CMV PCR 41,000copies/mL	Generic criteria	CMV IgM + CMV IgG + Low avidity CMV IgG CMV PCR 19,000,000 copies/mL	CMV IgM + CMV IgG + CMV PCR 119,611copies/mL
Diagnostic criteria for HLH	Fever Splenomegaly Bicytopenia Ferritin 1,314 ng/mL BMB positive sIL-2R 1058 U/mL	Fever, splenomegaly, Bicytopenias, Ferritin 883 ng/mL Hyponatremia transaminitis BMB positive	In accordance with HLH-2004 criteria BMB+, no other details available	Fever, Hepatomegaly, Bicytopenia Hypofibrinogenemia Ferritin 40,000 ng/mL	HLH 2004 all 8 criteria fulfilled Ferritin 10,000 ng/mL sIL-2R 3611U/mL
Treatment	Cyclosporin A and G-CSF	IV immunoglobulin for 4 days	No details	VGC, GCV, steroids	GCV, steroids
Outcome	Discharged day 14, recovered	Discharged day 15, recovered	No details	Discharged on day 47, recovered Readmitted after 1 Week, Discharged on day 40, recovered	Discharged on day 58, recovered

G-CSF = Granulocyte colony stimulating factor, sIL-2R = serum soluble interleukin-2 receptor, VGC = Valganciclovir, GCV = Ganciclovir.

**Table 2**  
HLH-2004 diagnostic criteria.

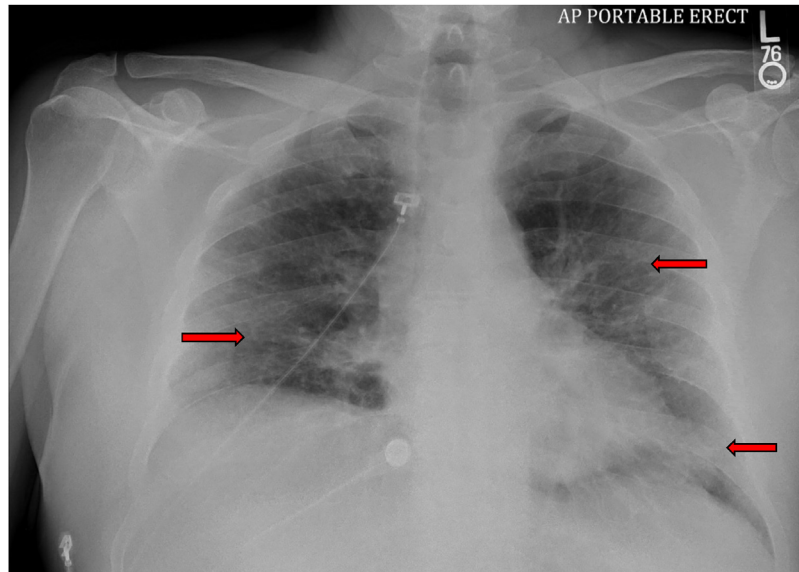
The diagnosis of HLH can be established if Criterion 1 or 2 is fulfilled
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)
Fever
Splenomegaly
Cytopenias (affecting $\geq 2$ of 3 lineages in the peripheral blood)
Hemoglobin $< 90$ g/L (hemoglobin $< 100$ g/L in infants $< 4$ wk)
Platelets $< 100 \times 10^9/L$
Neutrophils $< 1.0 \times 10^9/L$
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides $\geq 3.0$ mmol/L (ie, $\geq 265$ mg/dL)
Fibrinogen $\leq 1.5$ g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes.
No evidence of malignancy.
Low or no NK cell activity (according to local laboratory reference)
Ferritin $\geq 500$ $\mu\text{g/L}$
sCD25 (ie, soluble IL-2 receptor) $\geq 2400$ U/mL
<b>Supportive evidence includes:</b>
Cerebral symptoms with moderate pleocytosis and/or elevated protein
Elevated transaminases
Elevated bilirubin
Elevated LDH
Elevated D-dimer

## Case presentation

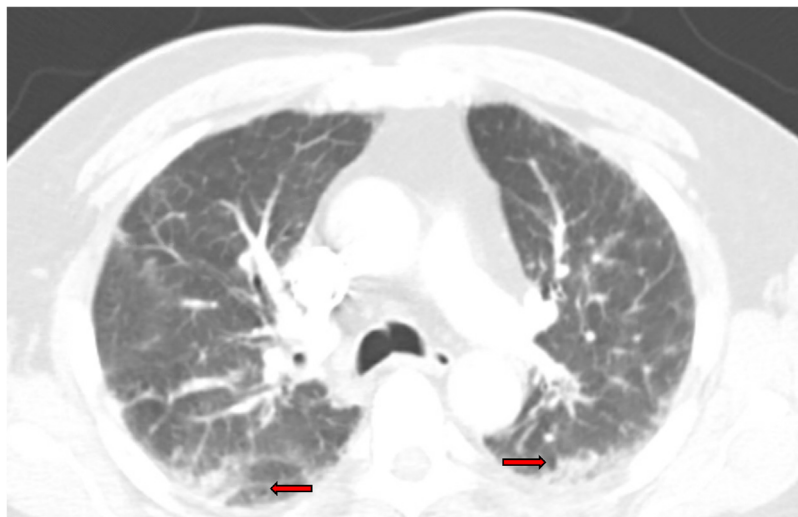
A 72-year-old white male with a past medical history of hypertension, hyperlipidemia, eczema, and glaucoma presented with worsening dyspnea, fever, and dry cough for two weeks. Before the above presentation, he had flu-like symptoms with no dyspnea for two weeks. His medication list included simvastatin, cetirizine, latanoprost eye drops. He had no history of any medication allergies or substance abuse. He endorsed sick contact exposure while babysitting his grandchildren (one of them had a rash and another viral pneumonia) with no recent travel or surgical history. His treatment was conservative with self-quarantine, hydration, and acetaminophen as needed for the initial two weeks. During the third week, due to persistent symptoms and worsening dyspnea, he presented to an urgent care clinic where testing for flu antigen, strep throat, and the nasopharyngeal (NP) Coronavirus disease 2019 (COVID-19) were negative. He was treated with five days of oral azithromycin and amoxicillin-clavulanic acid for community-acquired bacterial pneumonia with no improvement.

Given the worsening of his symptoms, he presented to a local emergency department four days later. Clinical examination revealed tachypnea of 28 breaths per minute, tachycardia of 104 beats per minute, stable blood pressure, a temperature of 37.3° Celsius (C), and oxygen saturation of 95 % on room air. Physical examination revealed facial flushing, sinus tachycardia, and bilateral coarse lung crackles. Laboratory evaluation revealed leukocytosis of 12,750/mL with a normal differential, sodium of 130 mEq/L, creatinine of 1.2 mg/dL, AST (aspartate aminotransferase) of 109 U/L, ALT (alanine aminotransferase) of 140 U/L, and an elevated D-dimer of 1130 ng/mL. Other studies included a normal creatinine kinase, brain natriuretic peptide (BNP), international normalized ratio (INR), and lactic acid. Imaging studies chest x-ray and computed tomography (CT) of the chest with contrast demonstrated mild bilateral interstitial infiltrates with small bilateral pleural effusions (Figs. 1–3).

On admission, he was placed on airborne precautions due to concern for COVID-19. Blood work showed leukocytosis of 13,000/mL with neutrophils of 78 %, bands of 13 with lymphocytes of 8 %. Blood work also revealed a mildly elevated procalcitonin with hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and negative respiratory pathogen panel and COVID-19 test (Table 3). Urine legionella and streptococcal antigens were negative. He continued to be febrile with a high of 39.8 °C with chills and diaphoresis. He was initiated on empiric intravenous (IV) antibiotics vancomycin and cefepime for pneumonia treatment and two liters' fluid restriction per day. Due to worsening dyspnea and hypoxia on day three, he needed 3 L of oxygen to maintain saturation  $> 90$  %. CT chest with contrast revealed interval worsening of his infiltrates with no pulmonary embolism (Figs. 4 and 5). Oral azithromycin was added to his empirical regimen for atypical pneumonia coverage. An increasing leukocytosis of 14,500/mL and the presence of five smudge cells and atypical lymphocytes on a peripheral smear (PS) prompted a hematology consult. There was no evidence of malignancy or hemophagocytosis on PS review. Over the next four days, he completed azithromycin with symptom improvement. However, by day nine, his leukocytosis was 24,600/mL with a fever of 38.7 °C, harsh dry cough, peripheral edema, and sinus tachycardia. Blood cultures drawn were negative with normal urine analysis, and a chest x-ray showed no significant changes. CT abdomen and pelvis revealed splenomegaly of 18 cm and multiple splenic infarcts with no splenic vein or arterial thrombosis (Fig. 6).



**Fig. 1.** Chest x-ray portable reveals patchy bilateral infiltrates without improvement compared to prior chest x-ray obtained on 4/13/20 at the outside hospital.

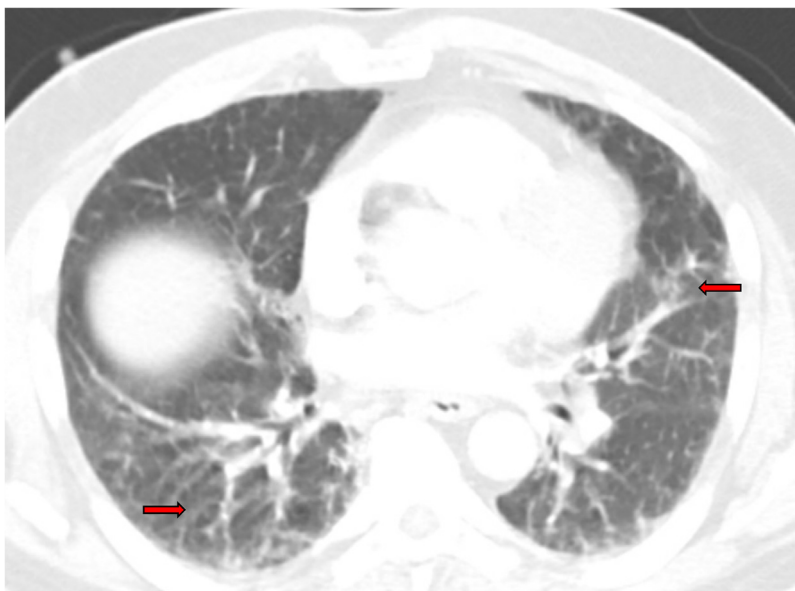


**Fig. 2.** CT Chest with contrast revealed bilateral lower lobe interstitial infiltrates.

By day 11, leukocytosis remained elevated at 24,000/mL with an elevated interleukin-6 at 35.5 pg/mL. Given the leukocytosis, he was restarted on azithromycin. Due to elevated serum ferritin and D-dimer, the hematology team recommended workup for suspected HLH (Table 3), in addition to a Positron emission tomography (PET) CT to rule out malignancy with a tick-borne illness panel due to recent history of trekking in the woods. A Pulmonology consult for pneumonitis on day 11 recommended additional workup, which unfolded a normal transthoracic and transesophageal echocardiogram. Repeat blood cultures and NP COVID-19 testing were negative; BNP, C-reactive protein, IgE (Immunoglobulin E), acute viral hepatitis panel, procalcitonin, fibrinogen, and INR were normal (Table 3). Due to worsening leukocytosis of 35,200/mL, doxycycline was initiated for tick-borne illness. PET- CT scan revealed progressive bilateral pulmonary infiltrates with left upper lobe progression suspicious of infection. The pretracheal lymph node size and metabolic activity showed an increase consistent with infection. An enlarged spleen with

multiple low metabolic activity lesions not indicative of any infection or neoplasm was observed.

A bronchoscopy on day 15 demonstrated minimal opaque sticky secretions in the left upper lobe. Immediately after the first pass for the transbronchial biopsy of the LUL, the patient developed a left pneumothorax, and only a scant LUL BAL and biopsy specimen was obtained. Further attempts at biopsy were aborted, and the procedure terminated prematurely. The LUL biopsy was negative for malignancy and infection. Left upper lobe (LUL) bronchoalveolar lavage (BAL) analysis showed total cells of 130, leukocytes of 45 /mL, erythrocytes of 85/mL, neutrophils of 88 %, lymphocytes of 10 % with negative bacterial, fungal, and mycobacterial cultures. The left pneumothorax was treated with a left chest tube and endotracheal intubation for respiratory support. BAL COVID 19 testing was negative and oral azithromycin and doxycycline were discontinued. The patient then developed a left knee lacy rash, which gradually improved. Chest x-ray still disclosed bilateral diffuse airspace opacities. Autoimmune workup, tick panel, and



**Fig. 3.** CT Chest with contrast revealed bilateral lower lobe interstitial infiltrates.

**Table 3**

Inpatient laboratory and imaging findings in a snapshot.

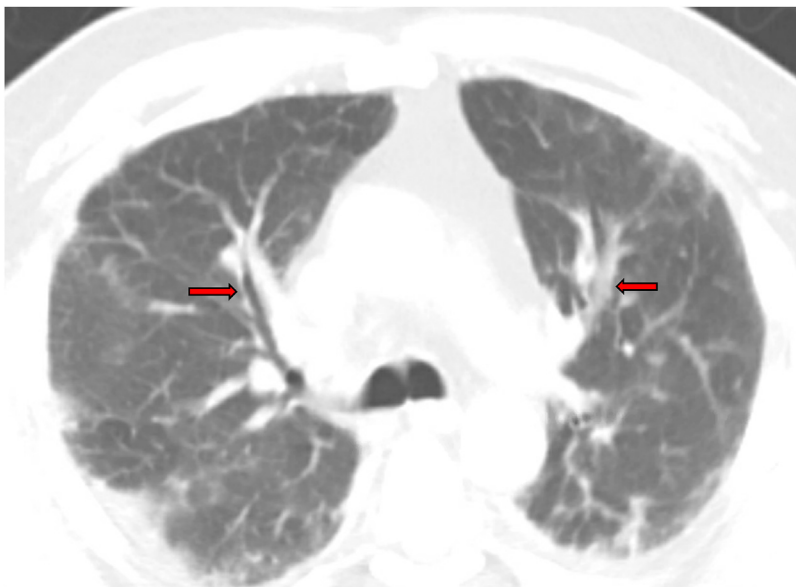
Laboratory test/Others	Result	Laboratory test/Imaging	Result
Temperature max	39.83 °C	AM serum cortisol	18.5 µg/dL
Ferritin	5603 ng/mL	IL-6 (Interleukin 6)	35.5 pg/mL
Triglycerides	250 mg/dL	CMV IgM	Positive 99.49 AU/mL ( $\leq 30$ )
CBC	Hemoglobin 9.7 g/dL Platelet count 169,000/mL	CMV IgG	Positive 2.80 U/mL ( $\leq 0.60$ )
D-dimer	1130 ng/mL	CMV PCR	29,235 IU/mL 50,284 copies/mL
Lactate dehydrogenase	459 U/L	EBV VCA IgM	Negative < 36 U/mL
sIL-2R (soluble interleukin-2 receptor)	13,023 pg/mL = 1472 U/mL (532–1891 pg/mL)	EBV VCA IgG	Positive 95.6 U/mL ( $\leq 18$ )
HIV (Human Immunodeficiency Virus)	Negative	Bronchial Alveolar Lavage (BAL) CMV PCR	664,962 IU/mL
Rheumatoid Factor (RF)	Negative	CSF CMV PCR	< 200 IU/mL
Anti-neutrophil Cytoplasmic Antibody (ANCA)	Negative	BAL cultures bacterial and fungal	Negative
Anti-nuclear antibody (ANA) screen	Negative	Rocky Mountain Spotted Fever, Lyme serology, Ehrlichia PCR	Negative
Nasopharyngeal and BAL COVID 19 test	Negative	Acute Viral Hepatitis panel	Negative
Serum sodium	127 mEq/L	Respiratory Pathogen Panel PCR	Negative
Urine sodium	47 mEq/L	Procalcitonin	049 ng/dL
Serum osmolality	273 mosm/kg	INR	1.3
Urine osmolality	477 mosm/kg	Transthoracic Echocardiogram Transesophageal Echocardiogram	No valvulopathy or Infective endocarditis
Thyroid-stimulating hormone level	3.14 uIU/mL	Splenomegaly	Present
Adrenocorticotropic hormone	44 pg/mL	Left Upper Lobe Lung Pathology Left Upper Lobe CMV stain	No cancer Negative

COVID -19 = Coronavirus disease 2019, CMV = Cytomegalovirus, EBV = Epstein-Barr virus, VCA = Viral capsid antigen, PCR = Polymerase chain reaction.

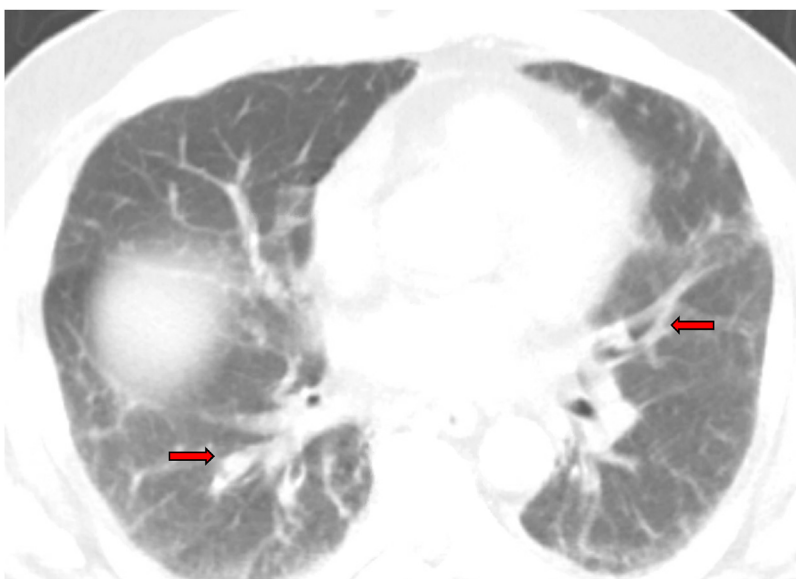
methicillin-resistant *Staphylococcus aureus* nasal screen were negative; thus, vancomycin was stopped. He was started on IV methylprednisolone with improvement in his leukocytosis. Serum triglycerides were within normal limits, and human immunodeficiency virus screening was negative. CMV and EBV serology were indicative of an acute CMV infection and a prior EBV infection (Table 3). The infectious disease team consulted for acute CMV pneumonitis on day 20 initiated him on iv ganciclovir (GCV) for suspected CMV pneumonitis. He was successfully extubated, followed by chest tube removal. On the 21 st day, due to confusion spells, a lumbar puncture was performed. Cerebrospinal fluid (CSF) analysis revealed glucose of 60 mg/dL, total protein of 101 mg/dL, total cells of 114 with leukocytes of 14/cmm, erythrocytes of 100

/cmm, neutrophils of 2%, lymphocytes of 81 %, and others of 17 %. CSF cryptococcal antigen, CSF meningitis multiplex polymerase chain reaction (PCR), and encephalitis panel were negative. Serum immunoglobulin quantification ruled out any deficiency, CT head showed no acute intracranial changes, and a chest x-ray showed no new changes.

After his hypoxia and fevers resolved, IV corticosteroids were changed to oral prednisone 60 mg daily. GCV was changed to oral valganciclovir (VGC) 900 mg orally twice daily. By day 24, prednisone was at 40 mg daily with an improvement in his dyspnea, and he was back on room air. Leukocytosis had resolved, and chest x-ray disclosed an improvement in bilateral interstitial infiltrates. sIL-2R (soluble interleukin-2 receptor), BAL CMV PCR



**Fig. 4.** CT Chest with contrast revealed interval increase in small amount of right upper lobe subsegmental atelectasis and small amount of bilateral dependent upper to midlung zone atelectasis.



**Fig. 5.** CT Chest with contrast revealed improved bilateral diffuse interlobular septal thickening suggestive of interstitial edema.

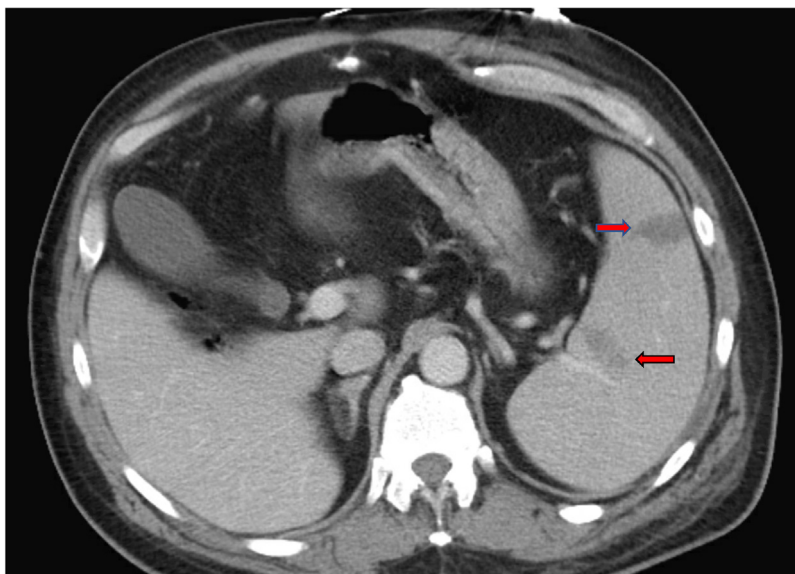
(Polymerase chain reaction), and blood CMV PCR returned elevated while the BAL lymphoma panel and CSF CMV PCR was negative (Table 3). The BAL sample was inadequate for CMV staining, whereas the LUL biopsy CMV stain was negative. He was diagnosed to have moderate secondary HLH due to CMV pneumonitis by the hematology team with a recommendation to treat the underlying cause. On day 26, the ophthalmologic evaluation did not disclose any retinitis. He was discharged home on oral VGC to complete three weeks of antiviral therapy and a tapering oral dose of prednisone.

At two weeks post-discharge, he had completed his antiviral therapy and oral prednisone with improvement in his symptoms. The lymphoma panel was negative. CMV blood DNA PCR quantitative was less than 200 IU/mL, EBV DNA PCR was high at 11,010 copies/mL. EBV viral load elevation was possibly due to reactivation from HLH induced immune suppression and oral

steroids. At four weeks, leukocytosis, AST, and ALT had returned to baseline with ferritin at 664 ng/mL, sIL-2R levels at 450 U/mL, CMV PCR was undetectable, and EBV PCR at < 200 copies/mL. The patient agreed to follow up with hematology as an outpatient with serial monitoring of EBV and CMV titers along with other parameters of secondary HLH.

### Discussion

HLH is a fatal disorder with an annual incidence of 1.2 cases per million patients per year [2]. The average time taken to diagnose HLH from symptom onset was 34.5 days [4]. HLH occurs due to the failure of the immune system to clear the antigenic precipitant. This failure leads to a lack of de-escalation of the inflammatory response resulting in a cytokine storm. In an immunocompetent host, antigenic stimuli due to an infection or malignancy result in



**Fig. 6.** CT Abdomen and pelvis revealed splenomegaly of 18 cms, multiple splenic infarcts with no Splenic arterial or venous thrombosis.

Th1 immune response. Th1 response elicits cytokines' secretion such as interferon-gamma, tumor necrosis factor-alpha, and granulocyte-macrophage colony-stimulating factor. These cytokines activate the cytotoxic lymphocytes and natural killer cells (NK cells) to eliminate the target cells by releasing perforin and granzyme granules at the synaptic site. In primary or familial HLH, most reported genetic defects culminate in inadequate perforin levels or improper granule exocytosis. In acquired or secondary HLH, the involved processes are multiple that require further detailed explanation [5]. These various factors include single nucleotide polymorphisms in genes responsible for immune response, an asymmetry between target cells and immune effector cells, viral or cytokine hindrance of cytotoxic function, low NK cells, and temporal immune inactivity by immunosuppressive drugs [5]. Ultimately this leads to a cytokine storm and death of the innate and adaptive immune system cells by apoptosis.

The Histiocyte Society, based on pediatric clinical data, endorsed the HLH 2004 diagnostic criteria for HLH diagnosis. Based on expert opinion, they have been used in adults to make a diagnosis [6]. For adults, the criteria consist of two clinical findings (fever, splenomegaly) and seven laboratory criteria (cytopenias, hyperferritinemia, hypertriglyceridemia or hypofibrinogenemia, and hemophagocytosis), including three special tests (genetic testing, NK cell function, and sIL-2R or soluble CD25 [sCD25]) [6]. The genetic testing is rarely done in adults as the incidence is around 7% in the United States [6]. Patients need to meet  $\geq$  five of the eight diagnostic criteria. In specific clinical scenarios, when five criteria are not satisfied, but HLH consideration is substantial; then treatment can be started [6]. HLH 2004 criteria are specific for children. At the time of 2004 criteria set up, serum ferritin  $>$  500 ng/mL had a sensitivity of 84% with no documented specificity [7]. In adults, ferritin levels  $\geq$  3000  $\mu$ g/L are not predictive of HLH, whereas, in the pediatric population levels  $\geq$  10,000  $\mu$ g/L are 90% sensitive and 96% specific [7]. In adults, there is no established upper limit for ferritin that is specific for HLH [7,8]. In a recent retrospective study in 2019, they reviewed 1055 adult patients with serum ferritin  $>$  5000 ng/mL for HLH. The ideal ferritin breakpoint for HLH diagnosis was 16,000 ng/mL (sensitivity 79.4%, specificity 79.2%, positive predictive value (PPV) 20.9%, and negative predictive value (NPV) 98.2%). They concluded that baseline ferritin levels utilized in the diagnostic criteria are too small for clinical relevance and propose revising them to a higher

value [7]. They recommend revisiting ferritin and other criteria used in diagnosing adult HLH. Normal serum ferritin level  $<$  500 ng/mL essentially rules out secondary HLH giving it a high negative predictive value [7].

Despite the occurrence of cytokine storm in HLH, sIL-2R is the only cytokine marker as a part of the diagnostic criteria. In the pediatric population, sIL-2R levels  $\geq$  2400 U/mL revealed a sensitivity of 88%–93% and a specificity of 100% [9]. Two recent retrospective studies reviewed sIL-2R sensitivity and specificity in the diagnosis of HLH in adults. In the first study carried out in 2017, (03/2012–04/2017), they reviewed measured sIL-2R in 78 consecutive adults (2012–2017) suspected of HLH. The results validated that sIL-2R is a sensitive test, and at the threshold mark used in HLH 2004, levels  $\geq$  2400 U/mL revealed a sensitivity of 100% and specificity of 63%. Clinical data supported a superior threshold of 2515 U/mL for HLH diagnosis with a sensitivity of 100% and a specificity of 72.5% [9]. This study also suggested sIL-2R levels  $\leq$  2400 U/mL as a sensible rule out (sensitivity, 100%), and levels  $>$  10,000 U/mL as a reasonable rule in (specificity, 93%) for HLH in adults [9]. This study demonstrated the superiority of sIL-2R over ferritin as a diagnostic marker. sIL-2R levels  $>$  10,000 U/mL were not associated with a worse prognosis [9]. In the second study done in 2019, they analyzed measured sIL-2R from 132 adults (01/2009–07/2019) suspected of HLH. The HLH 2004 criteria cutoff of sIL-2R  $\geq$  2400 U/mL yielded a sensitivity of 89.2% and specificity of 38.8%. They concluded that sIL-2R is a fundamentally flawed test for secondary HLH diagnosis in adults [10]. It performs poorly in discriminating secondary HLH from other pro-inflammatory conditions. They recommended the reevaluation of the sIL-2R role in this setting [10]. Similarly, bone marrow biopsy reliability in HLH diagnosis is problematic as bone marrow haemophagocytosis has a specificity of 60% [3]. Bone marrow biopsy recommendation is only in the absence of other supportive criteria or when malignancy is suspected.

As per HLH 1994, treatment guidelines (expert opinion) recommend using a short course of corticosteroids with or without IVIG (intravenous immunoglobulin) in patients with less severe disease or improving clinical manifestations [6]. If EBV is the causative agent, then the recommendation is to add rituximab to clear the viral reservoir. In EBV-HLH, the use of etoposide has improved survival significantly. In cases with persistently higher or upward-trending EBV counts, consider stem cell transplantation

[6]. No randomized clinical trial data exists to demonstrate the effectiveness of the above mentioned therapeutic modalities in immunocompetent adults with infection-associated HLH. In healthy adults, the data comes from case reports and extrapolation of data from CMV and EBV infection-associated HLH treatment in solid organ transplant patients [11]. IVIG has improved the prognosis in viral infection-associated HLH by its anti-inflammatory activity [11]. Anti HLH therapy, once initiated, needs to be monitored by repeating ferritin, sIL-2R, cell counts, and viral loads at scheduled intervals to assess treatment response [6]. In infection-associated HLH, the treatment of the infectious agent is significant but not adequate by itself. CMV-specific antiviral therapy includes the following Antivirals: GCV, VGC, foscarnet, cidofovir, and letermovir.

Among the secondary causes of HLH, infections account for close to 50 % of the cases [4]. Infective causes include viruses, bacteria, fungi, and parasites. Viruses are the most common infective agents responsible for HLH. EBV is responsible for most of the viral infections causing HLH, with most of these cases reported from Asia [1]. In Japan, the incidence of EBV-associated HLH is 0.4 cases per million persons [1]. Infection-associated HLH is highly underrecognized and associated with a higher mortality rate of 47 % [4]. In infectious causes, worse prognostic indicators are age greater than 50 years, disseminated intravascular coagulation, fever with no resolution after three days post HLH diagnosis [4]. CMV-associated HLH is a well known instigator of HLH in immunosuppressed or children. CMV infection is common during a patient's lifespan, and in most cases, the presentation is subclinical. Uncommonly, it can present as infectious mononucleosis in adults. The laboratory deviations frequently observed are hemolytic anemia, thrombocytopenia, reactive lymphocytosis, and elevated aminotransferases. CMV is an infrequent cause of HLH in the immunocompetent adult population. A review of medical literature via PubMed reveals only five described prior case reports (Table 1). Our case is the sixth case, and the second one in the United States; among the remaining four, two are from Asia and Europe, respectively. On reviewing these case reports, the average age is less than 50 years, and one of them had a functional immune deficiency attributed to poorly controlled diabetes mellitus. The first case therapy was with cyclosporin A and granulocyte colony-stimulating factor [12], whereas the second one was with IVIG [11]. With no real data on the third case, treatment of the fourth and fifth was with antivirals and steroids [3,13]. Only in two case reports was the specific antiviral therapy used for treatment. CMV disease therapy in immunocompetent hosts is not substantiated. The safety and effectiveness of IV GCV and oral VGC in the treatment of CMV disease in healthy individuals is unsettled. Despite no clinical data, it has been used in immunocompetent patients with successful outcomes, as noted in multiple case reports [14]. One reason which justifies its use in CMV-associated

HLH is the degree of immunosuppression observed in these patients by the time of diagnosis due to cytokine storm.

Our patient fulfilled only three of the HLH criteria due to the presence of fever, splenomegaly, elevated serum ferritin. He did not undergo bone marrow biopsy or NK cell activity or genetic testing. HLH 2004 criteria have not been validated yet in adults due to conflicting results with elevated sIL-2R levels, and high serum ferritin levels that do not correlate with specificity. As per the HLH guidelines on occasion, due to strong diagnostic consideration, treatment can be initiated with no criteria fulfillment. He did not qualify for cytopenia as per the strict criteria definition; however, his hemoglobin dropped from 15.5–9.7 mg/dL at the lowest and then recovered. His absolute neutrophil count was 1562, indicative of grade 1 neutropenia, and total lymphocyte count was 870, indicative of lymphopenia. HScore (Table 4) for the reactive hemophagocytic syndrome was 200 points, indicative of 80–88 % HLH probability. Regarding supporting evidence for HLH, he had an elevated LDH, ALT, AST, D-dimer, CSF protein, CSF cells, and total bilirubin of 2.4 mg/dL (Table 2). The ratio of sIL-2R to ferritin levels above 2.0 helps to distinguish lymphoma-associated HLH from other etiologies of HLH [9]. In our patient, the ratio was 2.32, but our patient had no clinical evidence of lymphoma. Due to HLH-induced suppression, our patient had EBV reactivation at two weeks postdischarge with a viral load of 11,010 copies/mL while the CMV viral load was < 200 IU/mL. At four weeks, patients' serum ferritin had improved to 664 ng/mL with undetectable CMV and a EBV viral load < 200 copies/mL and a sIL-2R at 450 U/mL. He responded appropriately to antivirals and steroids with improvement in his symptoms resulting in HLH resolution. As our patient developed pneumothorax during the bronchoscopy, inadequate biopsy, and BAL specimens from LUL were obtained for CMV staining. The LUL biopsy specimen was reported by the lab to be minimal, which diminished its yield for the CMV staining. Due to the low specificity of flow cytometry for NK cells and the invasive nature of the bone marrow biopsy, both were not recommended by the consultant hematologist in our elderly intubated patient. A longitudinal study in transplant patients revealed the inability of quantitative PCR CMV DNA in BAL to discriminate patients with and without CMV disease [15]. Longitudinal studies have an excellent value in transplant patients but not in healthy individuals as he was not on immunosuppressants and had no risk factors for reinfection. BAL CMV viral load > 5500 IU/mL had a sensitivity of 91 % and specificity of 75 % for CMV pneumonitis diagnosis [16,17]. In this study, the sensitivity remained > 90 % despite changes in viral load cutoffs for proven or probable CMV pneumonia in patients [16]. There are no clinical studies on the utility of using BAL CMV viral load to diagnose CMV pneumonia in a healthy individual. The clinical data on the ability to diagnose CMV pneumonia in transplant patients based on BAL CMV quantitative PCR in prior studies have not been consistent [15,16]. This inconsistency is due

**Table 4**  
Parameters and points in the HScore.

Parameter	No. of points (criteria for scoring)	Score attained by our patient, Total points = 200
Known underlying immunosuppression	0 (no) or 18 (yes)	0 (No)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)	49 (39.8°C)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)	23 (splenomegaly)
No. of cytopenias	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)	0 (none)
Ferritin (µg/L)	0 (<2000), 35 (2000–6000), or 50 (>6000)	35 (5603)
Triglyceride (mmol/L)	0 (<1.5), 44 (1.5–4), or 64 (>4)	44 (2.28)
Fibrinogen (g/L)	0 (>2.5) or 30 (≤2.5)	30 (2.45)
Aspartate aminotransferase (U/L)	0 (<30) or 19 (≥30)	19 (109)
Hemophagocytosis on bone marrow aspirate	0 (no) or 35 (yes)	0 (Not done)

to different test platforms, lack of standardization of CMV PCR kits, specimen types, and bronchoscopy methods. As the BAL viral load increased, so did the specificity [15,16]. Our patient's BAL viral load was 664,962 IU/mL, more than 100 times above the cutoff value. Based on the diagnostic criteria for CMV end-organ disease and BAL viral load involved, our patient qualified as probable CMV pneumonitis [17]. Our patient did have splenic infarcts with no evidence of any vascular thrombosis. Interestingly, our patient had hyponatremia due to CMV pneumonitis-induced osmoregulatory defect described in viral pneumonia [18]. Our case is the first reported CMV-associated HLH in an elderly immunocompetent male and the second case with hyponatremia due to CMV-associated HLH and the first case with SIADH.

## Conclusion

CMV-induced HLH in an immunocompetent patient is an infrequent occurrence. This case is the sixth reported instance, and the second one reported in the United States. Also, this is the second one to document the presence of CMV in blood and BAL by PCR. HLH simulates sepsis and other multiorgan dysfunction syndromes, so a high degree of suspicion is essential in detection. Ferritin still carries a very high negative predictive value but low specificity in adults. Two recent studies done on sIL-2R demonstrate conflict on its role as a biomarker for diagnosis. HLH 2004 criteria need revision in adults due to lack of specificity and to prevent the high mortality associated with it. Recent retrospective studies are few but encouraging. Additional research in secondary HLH due to infections is paramount due to the lack of evidence-based therapeutic data.

## Credit statement of author's contributions

Sachin M Patil, Michael P Hunter, Phillip Paul Beck, and Tarang Pankaj Patel worked on drafting, editing, and reviewing the manuscript that was prepared for submission and performed a literature review for this project. Sachin M Patil, Bran Andres Acevedo and William Roland were involved in the care of the patient being discussed. Bran Andres Acevedo, Jeremy Johnson and William Roland, as faculty advisors, contributed by assisting in reviewing and editing of this case report and provided project supervision and administration. We confirm that the manuscript has been read and approved by all named authors. We further confirm that all have approved the order of authors listed in the manuscript.

## Ethics approval and consent to participate

Care taken to ensure that all patient identifiers were removed in the process of creating this case report, and the patient was made aware of this case report.

## Consent for publication

Written and verbal informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Availability of data and materials

Not applicable

## Declaration of Competing Interest

The authors declare that they+ have no competing interests

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