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Case Report: Hemophagocytic lymphohistiocytosis after SARS-CoV-2 infection revealing clinically diagnosed stage IVB diffuse large B-cell lymphoma in quiescent adult-onset Still's disease

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Background: Adult hemophagocytic lymphohistiocytosis (HLH) may be triggered by infection, malignancy, or systemic inflammatory disease. Attribution is challenging when recent SARS-CoV-2 infection, quiescent adult-onset Still's disease (AOSD), and an occult B-cell clonal disorder coexist.

Case report: A 71-year-old man with AOSD controlled for 14 years on low-dose methotrexate developed persistent fever and fatigue after mild SARS-CoV-2 infection. He subsequently developed cytopenias, hyperferritinemia, markedly elevated lactate dehydrogenase, diffuse FDG-avid lymphadenopathy, hepatosplenomegaly, elevated soluble interleukin-2 receptor, reduced natural killer-cell activity, and bone marrow hemophagocytosis, fulfilling HLH criteria. Broad pathogen evaluation, including blood and bone marrow metagenomic next-generation sequencing, did not identify an alternative infectious trigger. Bone marrow histopathology did not show definite tumor cells; however, flow cytometry identified monoclonal mature B cells, and peripheral-blood smear high-throughput sequencing detected lymphoma-associated mutations including MYD88, CD79B, IGLL5, PRDM1, DTX1, DUSP2, and BTG1. Multidisciplinary consultation favored probable lymphoma-associated HLH with clinically diagnosed stage IVB diffuse large B-cell lymphoma. HLH-directed therapy followed by rituximab-based lymphoma-directed chemotherapy led to transient clinical improvement, but the patient later died from infectious complications.

Conclusion: Mild SARS-CoV-2 infection may act as a co-trigger or unmasking event rather than the sole cause of HLH. Persistent high lactate dehydrogenase and soluble interleukin-2 receptor, diffuse lymphadenopathy, clonal mature B cells, lymphoma-associated mutations, and negative broad pathogen testing should prompt evaluation for occult lymphoma-associated HLH.

KEYWORDS
adult-onset Still's disease, case report, diffuse large B-cell lymphoma, hemophagocytic lymphohistiocytosis, SARS-CoV-2

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome caused by ineffective cytotoxic immune responses, pathologic activation of T cells and macrophages, and cytokine-mediated tissue injury (1–5). In adults, HLH is most often secondary to infection, malignancy, systemic inflammatory disease, or treatment-related immune dysregulation (1, 2, 6–9). Distinguishing these triggers is clinically important because supportive immunosuppression alone is often inadequate when an underlying lymphoma is driving the inflammatory syndrome (6–10).

SARS-CoV-2 infection, adult-onset Still's disease (AOSD), and lymphoma can each produce fever, hyperferritinemia, cytopenias, hepatosplenomegaly, and cytokine-storm physiology (11–24). However, COVID-19-associated hyperinflammation, AOSD-associated macrophage activation syndrome (MAS), and lymphoma-associated HLH (LA-HLH) are not interchangeable diagnostic labels. Recent studies comparing cytokine-storm etiologies in hematologic malignancy and severe COVID-19 suggest distinct inflammatory patterns and outcomes (11, 12). Similarly, LA-HLH is increasingly recognized as a high-risk presentation that may precede or obscure the diagnosis of lymphoma (6–10). COVID-19 may also complicate DLBCL care and outcome interpretation in pandemic settings, reinforcing the need to separate viral inflammatory injury from lymphoma-driven hyperinflammation (25).

We report a patient with long-standing quiescent AOSD who developed HLH after mild SARS-CoV-2 infection. The diagnostic workup was notable for negative broad pathogen testing, non-diagnostic bone marrow histopathology, monoclonal mature B cells by flow cytometry, lymphoma-associated mutations by high-throughput sequencing, and diffuse FDG-avid lymphadenopathy. The case was ultimately managed as probable LA-HLH with clinically diagnosed stage IVB diffuse large B-cell lymphoma (DLBCL). The aim of this report is not to assert a single causal pathway, but to illustrate an immune-trigger attribution framework for adult HLH after SARS-CoV-2 infection.

Case description

A 71-year-old man was admitted to the Department of Rheumatology and Immunology, Peking University International Hospital, on September 25, 2023, because of fever for 17 days. On September 8, he developed fever to 38.4 °C with nasal congestion, rhinorrhea, sore throat, cough with white sputum, and marked fatigue. SARS-CoV-2 RNA testing was positive, whereas chest computed tomography did not show pneumonia. After cephalosporin-based therapy and anti-inflammatory treatment, fever temporarily resolved but fatigue persisted. On September 22, outpatient evaluation showed hemoglobin 108 g/L, albumin 37.8 g/L, alanine aminotransferase 54 U/L, total bilirubin 28.2 μmol/L, lactate dehydrogenase (LDH) 602 U/L, and ferritin 1427.1 ng/mL. Fever recurred that night, prompting admission.

His past medical history was notable for AOSD diagnosed 14 years earlier after intermittent high fever, rash, leukocytosis, and hyperferritinemia. He had responded to methylprednisolone and methotrexate, discontinued glucocorticoids within 3 months, and remained clinically stable on methotrexate 10 mg weekly. At admission, temperature was 36.5 °C, blood pressure 101/61 mmHg, pulse 81 beats/min, and respiratory rate 18 breaths/min. Physical examination was notable only for mild bilateral lower-limb edema and mild right-knee tenderness without swelling.

Initial laboratory testing revealed leukocytes 4.8 x 10^9/L, lymphocytes 16.8%, hemoglobin 85 g/L, platelets 80 x 10^9/L, LDH 959 U/L, fibrinogen 432 mg/dL, ferritin 1279.3 ng/mL, erythrocyte sedimentation rate 80 mm/h, and C-reactive protein (CRP) 105.24 mg/L. SARS-CoV-2 RNA had turned negative. Screening for cytomegalovirus, Epstein-Barr virus, tuberculosis, and fungal infection was negative. Blood and urine immunofixation were unremarkable, tumor markers were negative, and antinuclear antibody, rheumatoid factor, and antineutrophil cytoplasmic antibody tests were negative. Blood and bone marrow metagenomic next-generation sequencing (mNGS) did not detect a pathogen. Chest CT showed bronchiolitis but no typical COVID-19 pneumonia. Echocardiography, abdominal ultrasonography, urinary-system ultrasonography, and superficial lymph-node ultrasonography did not show a clear alternative diagnosis.

On the second hospital day, fever recurred to 39.3 °C with fatigue and anorexia. He received sequential azithromycin, ceftriaxone plus minocycline, moxifloxacin plus cefoperazone/sulbactam, and baloxavir marboxil. Because AOSD relapse was initially suspected, intravenous methylprednisolone 40 mg daily was given. Fever decreased to approximately 37.5 °C and CRP declined, but fatigue, anorexia, nausea, abdominal distension, exertional dyspnea, and generalized edema progressed. Anemia and thrombocytopenia persisted, while LDH, triglycerides, ferritin, and inflammatory indices increased. On hospital day 12, fever recurred to 38.3 °C, with marked conjunctival and generalized edema, oliguria, chest tightness, and inability to turn independently. Arterial blood gas analysis under FiO2 33% showed pH 7.44, PaO2 178 mmHg, PaCO2 28 mmHg, lactate 6.8 mmol/L, bicarbonate 19 mmol/L, and extracellular base excess -5.4 mmol/L, consistent with hyperlactatemia and mixed acid-base disturbance rather than isolated hypoxemic respiratory failure. NT-proBNP was 2436 pg/mL. Peripheral-blood smear showed 9% atypical large lymphocytes with loose chromatin, abundant deeply stained cytoplasm, and occasional vacuoles.

PET/CT demonstrated diffuse enlarged FDG-avid lymph nodes, including left supraclavicular, mediastinal, abdominal, and paraaortic nodes, together with hepatosplenomegaly and increased liver and spleen uptake (Figures 1A–E). Soluble CD25 was >10,000 pg/mL and natural killer (NK)-cell activity was reduced to 12.37%. Bone marrow morphology showed hemophagocytosis (Figures 1F–H); however, bone marrow histopathology did not reveal definite tumor cells. Bone marrow flow cytometry identified a small monoclonal mature B-cell population (0.6%). Peripheral-blood flow cytometry identified monoclonal mature B cells accounting for 1.33% of nucleated cells, with large forward scatter, strong CD45 expression, positivity for CD22, CD79b, CD20, FMC-7, and membrane/cytoplasmic kappa light chain, weak CD19 expression, and negativity for CD23, CD5, CD10, CD11c, CD103, CD25, CD34,

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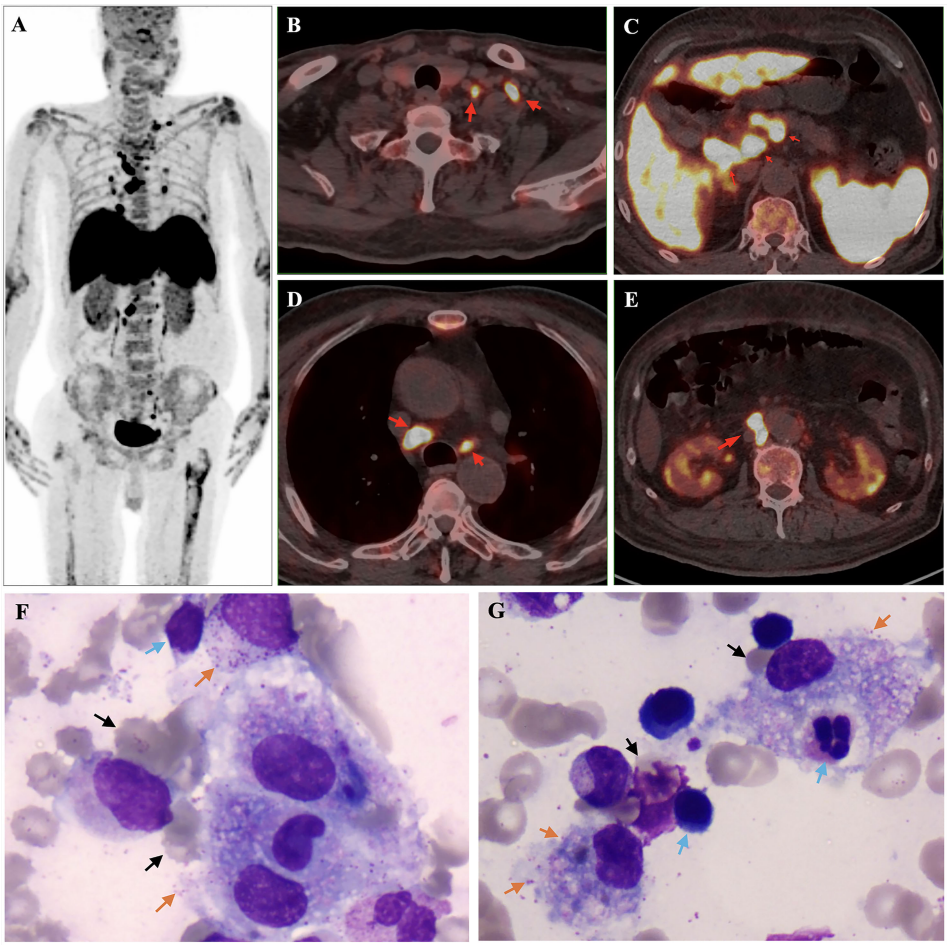

FIGURE 1
PET/CT and bone marrow morphology supporting the working diagnosis of probable lymphoma-associated HLH. **(A-E)** show PET/CT findings: the whole-body maximum intensity projection demonstrates multifocal FDG-avid disease **(A)**, and representative axial fused PET/CT images show FDG-avid lymphadenopathy in the left supraclavicular region (**B**, red arrows), abdomen/upper retroperitoneum (**C**, red arrowheads), mediastinum (**D**, red arrows), and para-aortic region (**E**, red arrow), with hepatosplenomegaly and increased liver/spleen uptake. **(F, G)** show Wright-Giemsa-stained bone marrow smears with hemophagocytosis; black arrows indicate erythrophagocytosis, blue arrows indicate engulfed nucleated cells/leukocytes, and orange arrows indicate platelet-sized or small cellular fragments. FDG, fluorodeoxyglucose; HLH, hemophagocytic lymphohistiocytosis.

CD38, CD71, and lambda light chain. High-throughput sequencing performed on a peripheral-blood smear detected MYD88, CD79B, IGLL5, PRDM1, DTX1, DUSP2, and BTG1 alterations. Dynamic changes in representative laboratory markers are shown in Figure 2. The revised hospitalization timeline, with admission designated as Day 0, is summarized in Table 1.

Diagnostic assessment, therapeutic intervention, and outcomes

The patient fulfilled HLH-2004 criteria by fever, splenomegaly, cytopenia affecting at least two lineages, hyperferritinemia, bone marrow hemophagocytosis, reduced NK-cell activity, and markedly elevated soluble CD25 (3). A *post hoc* HScore based on available contemporaneous data exceeded the diagnostic threshold of 169 proposed for reactive HLH; exact scoring was limited by incomplete same-day triglyceride, fibrinogen, and transaminase measurements (4, 26). The ferritin value met the ferritin component of the optimized HLH inflammatory (OHI) index, and soluble CD25 was markedly elevated; however, formal OHI classification was limited because the reported soluble CD25 unit was pg/mL rather than the U/mL threshold used in the original studies (7, 8). The diagnostic assessment is summarized in Table 2.

The multidisciplinary diagnosis was HLH with clinically diagnosed stage IVB DLBCL, resulting in probable LA-HLH. This diagnosis was clinical rather than histopathologically definitive. It was supported by diffuse FDG-avid lymphadenopathy, hepatosplenic involvement, progressive LDH elevation, severe soluble CD25 elevation, monoclonal mature B cells in marrow and blood, lymphoma-associated mutations, and transient improvement after HLH-directed and lymphoma-directed therapy. It was limited by the absence of a diagnostic lymph-node biopsy and by bone marrow histopathology that did not show definite tumor cells. The main competing triggers and their evidentiary weight are summarized in Table 3.

Methotrexate was discontinued. HLH-directed treatment was started with etoposide 100 mg/m2 weekly for 1 week and dexamethasone 10 mg/m2 for 2 weeks followed by tapering, according to

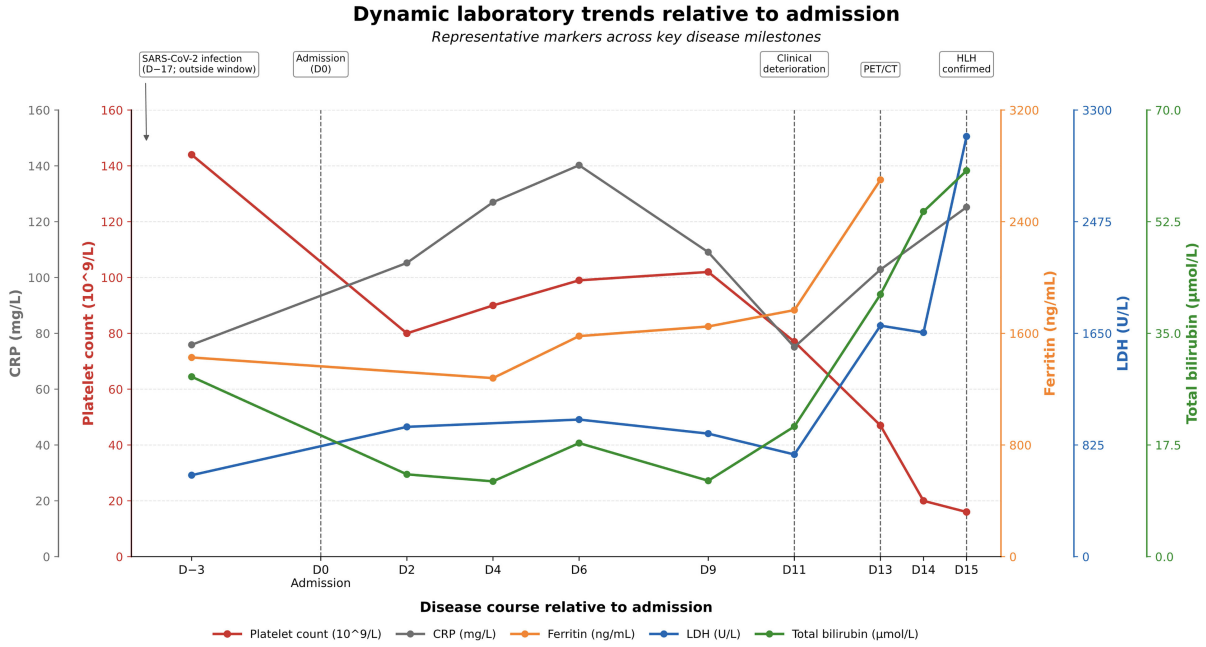

FIGURE 2
Dynamic laboratory trends relative to admission. Platelet count, C-reactive protein, ferritin, lactate dehydrogenase, and total bilirubin are plotted relative to the day of admission, which was defined as D0. The pre-admission laboratory point corresponds to D−3. SARS-CoV-2 infection occurred at D−17 and is shown as an out-of-window pre-admission event. Markers indicate measured values; successive measured values are connected to visualize the clinical trajectory, and no additional measurement points are imputed. Vertical dashed lines denote D0 admission, clinical deterioration, PET/CT evaluation, and HLH confirmation. CRP, C-reactive protein; LDH, lactate dehydrogenase; BM, bone marrow.

the HLH-94 principle. The patient then received a rituximab-based CHOP-like lymphoma-directed regimen consisting of rituximab 375 mg/m2, cyclophosphamide 0.6 g, vindesine 4 mg, and liposomal doxorubicin 20 mg. Fever resolved and general condition improved. After treatment, CRP declined to 2.4 mg/L and LDH to 344 U/L; ferritin remained elevated at 2414 ng/mL, fibrinogen was 155 mg/dL, D-dimer was 1047 ng/mL, and liver enzymes and creatinine were normal. He was discharged after clinical

TABLE 1 Revised hospitalization timeline and key findings.

Course (admission = Day 0)	Clinical findings	Laboratory/imaging findings	Therapeutic interventions	Diagnostic or management implication
14 years before admission	AOSD diagnosed after intermittent fever, rash, leukocytosis, and hyperferritinemia; disease remained clinically quiescent.	Historical leukocytosis and hyperferritinemia at AOSD onset.	Initial methylprednisolone and methotrexate; glucocorticoids tapered off within 3 months; methotrexate 10 mg/week maintained.	Long-standing quiescent systemic inflammatory disease with chronic immunomodulatory exposure.
Day -17 (September 8, 2023)	Fever to 38.4 °C with nasal congestion, rhinorrhea, sore throat, cough with white sputum, and fatigue.	SARS-CoV-2 RNA positive; chest CT without pneumonia.	Cephalosporin-based therapy and anti-inflammatory treatment.	Mild SARS-CoV-2 infection identified.
Day -3 (September 22, 2023)	Persistent fatigue; fever recurred later that night.	Hb 108 g/L, albumin 37.8 g/L, ALT 54 U/L, total bilirubin 28.2 μmol/L, LDH 602 U/L, ferritin 1427.1 ng/mL.	Outpatient evaluation; admission arranged after fever recurred.	Early systemic inflammatory and hematologic abnormalities.
Day 0 (September 25, 2023; admission)	Afebrile at admission; mild lower-limb edema and mild right-knee tenderness without swelling.	Hb 85 g/L, platelets 80 x 10^9/L, LDH 959 U/L, fibrinogen 432 mg/dL, ferritin 1279.3 ng/mL, CRP 105.24 mg/L; SARS-CoV-2 RNA negative; CMV, EBV, TB, fungal screening negative; chest CT showed bronchiolitis without typical COVID-19 pneumonia; blood and bone marrow mNGS negative.	Broad diagnostic evaluation and empiric anti-infective assessment.	Differential included infection, AOSD relapse/MAS, occult malignancy, and evolving HLH.

(Continued)

TABLE 1 Continued

Course (admission = Day 0)	Clinical findings	Laboratory/imaging findings	Therapeutic interventions	Diagnostic or management implication
Days 1-10	Fever to 39.3 °C, fatigue, anorexia, nausea, abdominal distension, exertional dyspnea, and progressive generalized edema.	CRP initially declined after corticosteroids, but anemia and thrombocytopenia persisted; LDH, triglycerides, ferritin, and inflammatory indices increased.	Sequential azithromycin, ceftriaxone plus minocycline, moxifloxacin plus cefoperazone/sulbactam, baloxavir marboxil; intravenous methylprednisolone 40 mg daily.	Incomplete steroid response and progression despite anti-infective therapy prompted expanded evaluation.
Day 11-13	Recurrent fever, marked conjunctival/generalized edema, oliguria, chest tightness, inability to turn independently, and clinical deterioration.	Lactate 6.8 mmol/L, NT-proBNP 2436 pg/mL, worsening thrombocytopenia, rising LDH/ferritin; peripheral-blood smear showed 9% atypical large lymphocytes; PET/CT showed diffuse FDG-avid lymphadenopathy, hepatosplenomegaly, and increased liver/spleen uptake.	Supportive care and urgent PET/CT; multidisciplinary evaluation intensified.	High suspicion for HLH and occult lymphoma/lymphoproliferative disorder.
Day 15 and subsequent evaluation	Persistent systemic illness with hyperinflammatory features.	sCD25 >10,000 pg/mL, NK-cell activity 12.37%, marrow hemophagocytosis; marrow histopathology without definite tumor cells; marrow/blood flow cytometry showed monoclonal mature B cells; peripheral-blood high-throughput sequencing showed lymphoma-associated mutations.	Methotrexate discontinued; HLH-directed treatment initiated with etoposide/dexamethasone, followed by rituximab-based CHOP-like chemotherapy.	HLH criteria fulfilled; multidisciplinary team favored probable LA-HLH with clinically diagnosed stage IVB DLBCL.
After treatment and follow-up	Fever resolved and general condition improved; discharged after stabilization; died approximately 1 month later from viral encephalitis and fungal pneumonia.	After treatment, CRP declined to 2.4 mg/L and LDH to 344 U/L; ferritin remained elevated at 2414 ng/mL.	HLH-94-based therapy and rituximab-based CHOP-like regimen; post-discharge treatment for infectious complications was unsuccessful.	Transient inflammatory control followed by fatal infectious complications.

Admission is designated as Day 0. Clinical findings, laboratory/imaging findings, therapeutic interventions, and diagnostic/management implications are separated to improve readability. AOSD, adult-onset Still's disease; BM, bone marrow; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; FDG, fluorodeoxyglucose; Hb, hemoglobin; HLH, hemophagocytic lymphohistiocytosis; LA-HLH, lymphoma-associated hemophagocytic lymphohistiocytosis; LDH, lactate dehydrogenase; mNGS, metagenomic next-generation sequencing; NK, natural killer; PET/CT, positron emission tomography/computed tomography; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sCD25, soluble CD25; TB, tuberculosis.

stabilization. Approximately 1 month after discharge, he died from viral encephalitis and fungal pneumonia that were refractory to treatment.

Discussion

This case highlights a common but underemphasized problem in adult HLH: trigger attribution when several plausible inflammatory drivers coexist. The patient had recent SARS-CoV-2 infection, a remote history of AOSD treated with methotrexate, and evidence of an occult mature B-cell clonal disorder. The strongest immediate diagnosis was HLH, whereas the most likely driver was probable LA-HLH associated with clinically diagnosed stage IVB DLBCL. The key lesson is that HLH after SARS-CoV-2 infection should not automatically be labeled COVID-19-associated HLH when the viral illness is mild and competing lymphoma-related signals are present.

Compared with previously reported COVID-19-associated HLH cases, the present case had several distinguishing features. Reported COVID-19-related HLH has often been described in acute or post-acute settings with marked systemic inflammation, frequently in severe COVID-19 or with pulmonary involvement, whereas our patient had a mild upper-respiratory syndrome, absent COVID-19 pneumonia, and negative SARS-CoV-2 RNA at admission (11–18, 27, 28). Conversely, the late emergence of high LDH, diffuse FDG-avid lymphadenopathy, hepatosplenomegaly, markedly elevated soluble CD25, monoclonal mature B cells, and lymphoma-associated mutations was more consistent with the clinical pattern of LA-HLH (6–10). Mechanistically, the three candidate backgrounds may converge on a shared cytokine-amplification network: SARS-CoV-2 can activate innate and T-cell responses; Still's disease/MAS is characterized by IL-1/IL-6/IL-18/interferon-gamma-related macrophage activation; and lymphoma can provide persistent tumor-driven antigenic stimulation, T-cell/macrophage activation, and soluble IL-2 receptor release (1, 5, 18, 19, 29–31). We do not infer *de novo* viral lymphomagenesis from this single case. A more cautious interpretation is that recent SARS-CoV-2 infection and the background of AOSD/methotrexate exposure may have lowered the threshold for HLH, while an occult aggressive B-cell clonal disorder was the dominant driver once the hyperinflammatory syndrome became self-sustaining.

COVID-19 can produce cytokine-storm physiology and has been reported as a trigger of secondary HLH (11–18, 27, 28). Nevertheless, this patient had mild upper-respiratory COVID-19 symptoms, no typical COVID-19 pneumonia on initial imaging,

TABLE 2 Diagnostic assessment for HLH and probable lymphoma-associated HLH.

Domain	Finding in this patient	Interpretation
HLH-2004 criteria	Fever, splenomegaly, cytopenia in ≥2 lineages, ferritin >500 ng/mL, bone marrow hemophagocytosis, reduced NK-cell activity, and sCD25 >10,000 pg/mL.	Diagnostic criteria for HLH fulfilled.
HScore	Available data included immunosuppression, fever, hepatosplenomegaly, two-lineage cytopenia, ferritin >2000 ng/mL at deterioration, hypertriglyceridemia, and marrow hemophagocytosis.	Post hoc score exceeded the 169 threshold; exact value limited by incomplete same-day triglyceride, fibrinogen, and AST data.
OHI index	Ferritin >1000 ng/mL and markedly elevated sCD25.	Suggestive of malignancy-associated HLH biology, but formal OHI application limited because sCD25 was reported in pg/mL, not U/mL.
Infectious assessment	SARS-CoV-2 RNA positive before admission but negative on admission; CMV, EBV, TB, fungal screening negative; blood and bone marrow mNGS negative.	No additional pathogen identified; occult infection could not be completely excluded.
Lymphoma/LPD assessment	Diffuse FDG-avid lymphadenopathy and hepatosplenic uptake; monoclonal mature B cells in marrow and blood; MYD88, CD79B, IGLL5, PRDM1, DTX1, DUSP2, and BTG1 alterations.	Supported occult mature B-cell clonal lymphoproliferative disorder/clinically diagnosed stage IVB DLBCL.
Pathologic limitation	Bone marrow histopathology did not show definite tumor cells; no diagnostic lymph-node biopsy or EBER study was available.	DLBCL was a multidisciplinary clinical diagnosis rather than histopathologically confirmed disease.

The table maps the patient's findings to HLH-2004 criteria, HScore/OHI considerations, infection exclusion, lymphoma/LPD evidence, and the key histopathological limitation.
AST, aspartate aminotransferase; CMV, cytomegalovirus; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; EBER, Epstein–Barr virus-encoded RNA; FDG, fluorodeoxyglucose; HLH, hemophagocytic lymphohistiocytosis; LPD, lymphoproliferative disorder; mNGS, metagenomic next-generation sequencing; NK, natural killer; OHI, optimized HLH inflammatory index; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sCD25, soluble CD25; TB, tuberculosis.

and negative SARS-CoV-2 RNA on admission. Blood and bone marrow mNGS did not reveal another infectious trigger, which reduced but did not eliminate the probability of occult infection in an immunosuppressed host. Recent studies suggest that severe COVID-19 with high HScore represents a specific high-risk subgroup, and cytokine storms associated with malignancy-related HLH differ biologically and prognostically from COVID-19 cytokine storm (11, 12). In this context, SARS-CoV-2 infection is best interpreted as a possible co-trigger or unmasking event rather than the sole explanation for the full syndrome.

AOSD-associated MAS was also considered. AOSD and systemic juvenile idiopathic arthritis are now commonly framed within the broader Still's disease spectrum, and MAS remains one of the most serious complications (19–24, 29–31). However, the patient had been clinically quiescent for 14 years and lacked typical early features of active AOSD, including evanescent rash, prominent

TABLE 3 Attribution of potential HLH triggers.

Potential trigger	Evidence supporting	Evidence against or limitation	Overall attribution
SARS-CoV-2 infection	Temporal association; fever and hyperferritinemia after positive SARS-CoV-2 RNA.	Initial infection was mild; no typical COVID-19 pneumonia; SARS-CoV-2 RNA negative at admission; progressive lymphoma-related signals emerged.	Possible co-trigger or unmasking event, not sufficient as sole cause.
Other occult infection	Older age, methotrexate exposure, corticosteroid and chemotherapy exposure increased susceptibility.	CMV, EBV, TB, fungal screening negative; blood and marrow mNGS negative before HLH-directed therapy.	Reduced probability but not completely excluded.
AOSD-associated MAS	Remote AOSD history; fever and hyperferritinemia overlapped with MAS.	AOSD quiescent for 14 years; no early rash, leukocytosis, prominent transaminase elevation, or typical flare pattern; progression despite methylprednisolone.	Considered but less likely dominant trigger.
LA-HLH/clinical DLBCL	High LDH and sCD25, diffuse FDG-avid lymphadenopathy, hepatosplenomegaly, clonal mature B cells, lymphoma-associated mutations, transient improvement after lymphoma-directed therapy.	No lymph-node histology; marrow histopathology non-diagnostic.	Most likely dominant driver; best described as probable LA-HLH with clinically diagnosed stage IVB DLBCL.
MTX/OII-LPD	Long-term methotrexate for AOSD; OII-LPD can mimic lymphoma and may be EBV related.	No tissue histology or EBER testing; clinical course required urgent treatment rather than observation after MTX withdrawal alone.	Important differential diagnosis; unclassifiable with available material.

The table contrasts evidence for and against SARS-CoV-2 infection, other occult infection, AOSD-associated MAS, LA-HLH/clinical DLBCL, and MTX/OII-LPD as contributors to the hyperinflammatory syndrome.
AOSD, adult-onset Still's disease; CMV, cytomegalovirus; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; EBER, Epstein–Barr virus-encoded RNA; FDG, fluorodeoxyglucose; HLH, hemophagocytic lymphohistiocytosis; LA-HLH, lymphoma-associated hemophagocytic lymphohistiocytosis; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; mNGS, metagenomic next-generation sequencing; MTX, methotrexate; OII-LPD, other iatrogenic immunodeficiency-associated lymphoproliferative disorder; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sCD25, soluble CD25; TB, tuberculosis.

leukocytosis, major transaminase elevation, or an initial Still's disease flare pattern. CRP decreased after methylprednisolone, but constitutional symptoms, cytopenias, LDH elevation, edema, oliguria, hyperferritinemia, and lymphadenopathy progressed. These features argued against uncomplicated AOSD relapse and favored a hidden hematologic process. Long-term methotrexate exposure also raised the possibility of other iatrogenic immunodeficiency-associated lymphoproliferative disorder (OII-LPD), including methotrexate-associated LPD (32–34). Because lymph-node histology and EBER testing were not available, OII-LPD could not be classified or excluded.

The evidence for lymphoma was clinically compelling but pathologically incomplete. Contemporary lymphoma classifications emphasize integrated morphology, immunophenotype, genetic data, and clinical context, and histopathology remains central to definitive DLBCL classification (35–38). Here, bone marrow histopathology did not show definite tumor cells, and no diagnostic lymph-node biopsy was obtained because of rapid deterioration. Accordingly, the manuscript deliberately uses 'clinically diagnosed stage IVB DLBCL' and 'probable LA-HLH' rather than 'pathologically confirmed DLBCL.' The diagnosis was supported by diffuse FDG-avid lymphadenopathy, hepatosplenic uptake, monoclonal mature B cells, and a mutation profile frequently encountered in aggressive B-cell lymphomas. MYD88 and CD79B co-alteration is particularly associated with the MCD genetic subtype of DLBCL, and genetic subtyping may have therapeutic implications; however, mutation positivity alone cannot establish histologic subtype and the exact MYD88/CD79B variants and variant allele fractions should be reported if available (39–44).

Therapeutically, this case also illustrates the narrow balance between controlling hyperinflammation and avoiding fatal infection. Adult HLH management often requires early etoposide-based therapy, corticosteroids, and rapid treatment of the underlying trigger (2, 6, 8–10). The transient improvement after HLH-94-based therapy and rituximab-based chemotherapy supports the working diagnosis, but the subsequent fatal viral and fungal infections underscore the vulnerability of older patients with HLH, prior immunosuppression, and lymphoma-directed treatment. For similar cases, early lymph-node biopsy when feasible, same-day HLH biomarker sampling, standardized soluble CD25 units, complete flow cytometry, EBV/EBER assessment, and molecular reporting with variant allele fractions may improve diagnostic confidence and allow earlier risk-adapted therapy.

Patient perspective

The patient's perspective could not be obtained because he died after the reported hospitalization. Written informed consent for publication of de-identified clinical details and images was obtained from the patient's legal representative before submission.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The study involving human data was approved by the Peking University International Hospital Institutional Review Board. The study was conducted in accordance with local legislation and institutional requirements. Written informed consent for publication of de-identified clinical details and images was obtained from the patient's legal representative.

Author contributions

TL: Data curation, Investigation, Validation, Writing – original draft, Writing – review & editing. JS: Investigation, Visualization, Validation, Writing – original draft, Writing – review & editing. SL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

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