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CASE REPORT

Ruxolitinib as an Effective Treatment for Hemophagocytic Lymphohistiocytosis Secondary to SARS-Cov-2 Infection: A Case Report

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome. SARS-CoV-2 infection can induce secondary HLH, as described in previous case reports, but diagnosis and treatment are challenging.

Case Study: We described an older male patient diagnosed with HLH related to previous SARS-CoV-2 infection. Fever was the only clinical manifestation initially but deterioration in clinical condition and laboratory parameters was observed during hospitalization. He responded poorly to classical therapy but was successfully treated with ruxolitinib.

Conclusion: Clinicians should be aware of the possibility of HLH secondary to mild SARS-CoV-2 infection and take timely therapeutic measures to inhibit an inflammatory factor storm. Ruxolitinib is a potential choice for COVID-19 related HLH.

Keywords: hemophagocytic lymphohistiocytosis, COVID-19, ruxolitinib, case report

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome caused by the proliferation of lymphocytes, macrophages, and $CD8^+$ T-cells, leading to massive cytokine release.[1] HLH is categorized into two forms, primary and secondary HLH.[2] The primary HLH occurs generally due to genetic defects resulting from autosomal recessive inheritance.[3] Secondary HLH (sHLH) is encountered in association with infectious causes, malignancy, rheumatological disorders and acquired immune deficiency states.[4] Viral infections, especially Epstein–Barr virus (EBV) and cytomegalovirus (CMV), are known as the most common infection triggers in sHLH.

The treatment of sHLH depends on treating the triggering factors. Since the pandemic of coronavirus disease 2019 (COVID-19), several sHLH cases associated with COVID-19 have been reported.[5] Currently, there is no standard treatment for inhibition of a systemic hyperimmune response that leads to multiorgan failure. The treatment with low dose ruxolitinib plus etoposide is a potential choice for COVID-19-related HLH.[6] Here, we present a case of HLH secondary to SARS-Cov-2 infection, which had rapid response to ruxolitinib.

Case Presentation

A 76-year-old man presented with three days of persistent fever not accompanied by other symptoms including cough, sore throat, fatigue or myalgia. Then he was diagnosed antigen-positive SARS-Cov-2 infection on 16 December 2022 during the epidemic of Omicron variant. He did not receive antiviral treatment and took antipyretics orally for 1 day by himself without visiting the hospital. In the next half month, his temperature was normal and loss of appetite was his main complaint. However, the fever reappeared on 3 January 2023, so he was admitted to our hospital on 5 January 2023. There were no complaints of cough, sputum, hemoptysis, abdominal pain, diarrhea, arthralgia and erythema. There was no history of environmental, occupational or long-term drug exposure. He had a medical history of hypertension and denied having autoimmune diseases.

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The patient was clinically stable at the time of admission. His oxygen saturation was 98% on room air; heart rate was 68 beats per minute; respiratory rate was 18 breaths per minute; temperature was 37.5°C; and blood pressure was 134/81mmHg. Blood tests including complete blood count, liver and renal function tests, coagulation tests and inflammation markers (C-reactive protein, interleukin-6 and erythrocyte sedimentation rate) were almost within normal limits, except the ferritin was increased (480.2 ug/L, normal range: 23.9–336.2 ug/L).

SARS-Cov-2 nasopharyngeal swabs were performed every three days and all of the tests were negative. Multiple cultures sets of blood, urine, and sputum were negative for bacteria, mycobacteria, or fungi. Twice next-generation sequencing of peripheral blood was negative. Viral infections (CMV, human immunodeficiency virus, hepatotropic viruses, herpes simplex virus, influenza virus, parvovirus, adenovirus and atypical respiratory pathogens) were promptly ruled out. EBV-DNA in peripheral blood lymphocytes was 1780 copies/mL (normal:500 copies/mL). EBV-DNA in plasma and EBV-IgM antibody were negative. No signs of malignant lesions were found in positron emission tomography-computed tomography (PET-CT) or bone marrow aspiration and biopsy. Hepatomegaly or splenomegaly were not detected by the ultrasound scan. Serum tumor markers, serum and urine immunofixation electrophoresis, ultrasound of superficial lymph nodes, and head MRI were performed and no obvious abnormalities were found except for the high serum carcinoembryonic antigen (CEA, 21ng/mL), which showed no significant change compared to last year's result (25.7ng/mL). He had a history of high CEA for five years and underwent gastrointestinal endoscopy one year before, but no signs of tumor were found. Rheumatologic tests showed the 1:320 positive antinuclear antibody, 1:100 positive anti-dsDNA antibody and slightly low C3 complement level (0.546g/L, normal range: 0.6–1.5g/L). Other indications of connective tissue disease, such as anti-ENA antibodies, antiphospholipid antibodies, direct Coombs test, ANCA and rheumatoid factor, were all negative.

During the hospitalization, a serious deterioration in clinical condition and laboratory parameters was observed (Table 1). His fever continued to increase and reached 39.8°C. We also noticed a change in his cognitive function. We found his leukocytes, hemoglobin and platelets were decreased; ferritin was raised; liver dysfunction, fibrinogen and natural killer (NK) cell activity decreased; and hemophagocytosis was present in bone marrow aspiration (Figure 1). Triglyceride and soluble interleukin-2 receptor (SIL-2R/sCD25) were normal. A diagnosis of sHLH was made according to HLH-2004 criteria, including presence of fever, hypofibrinogenemia, ferritin > 500ug/L, hemophagocytosis in bone marrow and low NK-cell activity (Table 2). H-score for sHLH showed an 80–88% probability of HLH, with a total of 192 points (Table 3).

From 22 January, he was treated with methylprednisolone 80mg/day intravenously for day 1 and day 2, sequential dexamethasone 20mg/day from day 3 to day 7, intravenous immunoglobulin 30g from day 1 to day 7 concomitantly, plus intravenous etoposide 180mg (100mg/m^2) on day 3. But the clinical presentation was not relieved, accompanied by

Table 1 Laboratory Parameters

Parameters	Ref.	Admission	Day 5	Day 13	Day 17	Day 20
White blood cell (10^9/L)	3.5–9.5	5.74	3.58	2.5	2.6	2.5
Neutrophil (10^9/L)	1.8–6.3	4.14	2.48	1.91	2	2
Lymphocyte (10^9/L)	1.1–3.2	1.06	0.73	0.43	0.4	0.3
Hemoglobin (g/L)	130–175	145	132	118	113	103
Platelet count (10^9/L)	125–350	179	125	108	93	83
Reticulocyte (10^9/L)	24–84	104.4	115.8	106.2	71.1	80.6
Ferritin (μg/L)	23.9–336.2	480.2	/	1124.6	1439.3	1451.9
Fibrinogen (mg/dL)	2–4	258	/	152	115	101
Triglycerides (mmol/L)	0.56–1.7	0.67	/	/	0.76	/
ALT (IU/L)	9–50	24	107	32	30	52
AST (IU/L)	15–40	30	55	25	25	42
Total bilirubin (umol/L)	1.7–20	20.6	25.4	21.8	16.3	16.9
D-dimer (mg/L)	<0.24	0.19	/	3.52	2.8	1.81

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

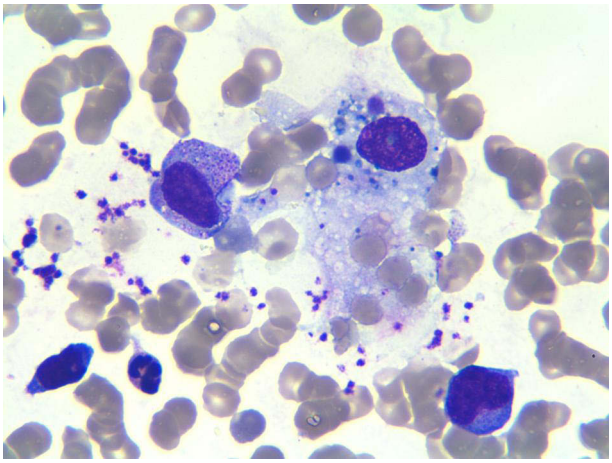

Figure 1 Bone marrow aspirate showing hemophagocytosis (Wright-Giemsa staining, ×1000).

persistent fever, decreasing white blood cells, platelets and fibrinogen and progressively increasing ferritin. Then the therapy was adjusted to ruxolitinib 10mg twice a day and methylprednisolone 60mg daily intravenously from day 8. The patient's symptoms improved significantly one week later, including the relief of fever and cognitive function, as well as the improvement of blood cell count, fibrinogen and ferritin (Figure 2). The patient tolerated ruxolitinib well and no severe side effects occurred during treatment such as hemorrhage, secondary infection, renal or liver dysfunction. He had continuously decreased leukocytes and platelets for several days after treatment, which may not have been due to

Table 2 Patient Parameters Within HLH-2004 Criteria

HLH-2004 Criteria	Patient's Values
1. Fever: ≥38.5C	39.8°C
2. Splenomegaly	No
3. Cytopenia[a] affecting ≥2 lineages	No, only one lineage meet criteria
4. Hypertriglyceridemia: fasting triglycerides >265 mg/dl OR hypofibrinogenemia: ≤150 mg/dl	Fibrinogen: 115mg/dl
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes	Bone marrow biopsy showed hemophagocytosis
6. Hyperferritinemia: ≥500 μg/L	2900 ug/L
7. Low or absent NK-cell activity	11.36% (Ref. ≥15.11%)
8. Elevated soluble IL-2R/CD25: ≥2400 U/mL	No

Note: [a]Defined as a hemoglobin level <90 g/L and/or a platelet level <100 × 10^9/L and/or a neutrophil level <1.0 × 10^9/L.

Table 3 Patient Parameters Within H-Score

Parameter	Points (Criteria for Scoring)	Patient's Values
Known underlying immunosuppression[a]	0 (No) or 18 (Yes)	No
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)	>39.4
Organomegaly	0 (No), 23 (Hepatomegaly or splenomegaly), or 38 (Hepatomegaly and splenomegaly)	No
No. of cytopenias[b]	0 (1 Lineage), 24 (2 Lineages), or 34 (3 Lineages)	2 Lineages
Ferritin (ug/L)	0 (<2000), 35 (2000–6000), or 50 (>6000)	2900
Triglyceride (mmol/L)	0 (<1.5), 44 (1.5–4), or 64 (>4)	<1.5
Fibrinogen (g/L)	0 (>2.5) or 30 (≤2.5)	≤2.5
Serum glutamic oxaloacetic transaminase (IU/L)	0 (<30) or 19 (≥30)	≥30
Hemophagocytosis features on bone marrow aspirate	0 (No) or 35 (Yes)	Yes

Notes: H-score: 192 points. [a]Human immunodeficiency virus positive or receiving long-term immunosuppressive therapy (ie, glucocorticoids, cyclosporine, azathioprine). [b]Defined as a hemoglobin level of ≤9.2 g/L and/or a leukocyte count of ≤5 × 10^9/L and/or a platelet count of ≤110×10^9/L.

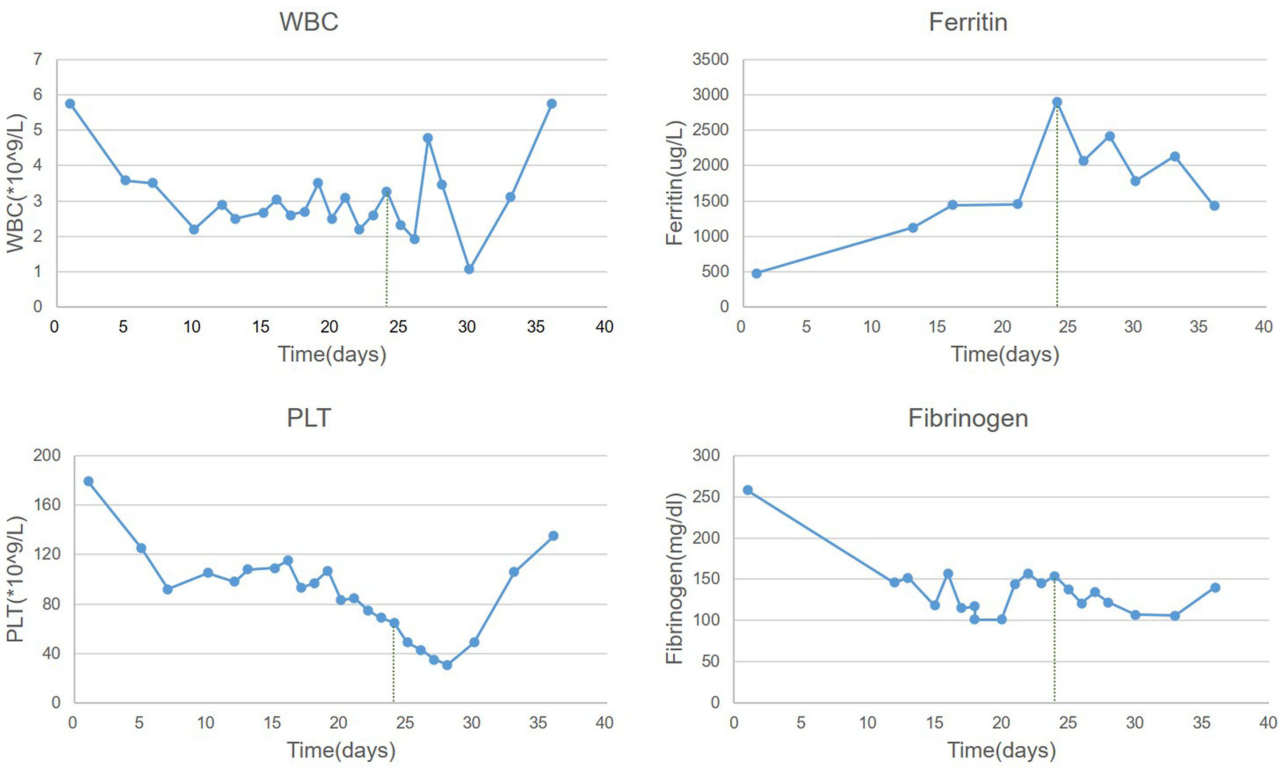

Figure 2 Change of laboratory parameters. The patient was treated with ruxolitinib on the 24th day after admission (green dotted line).

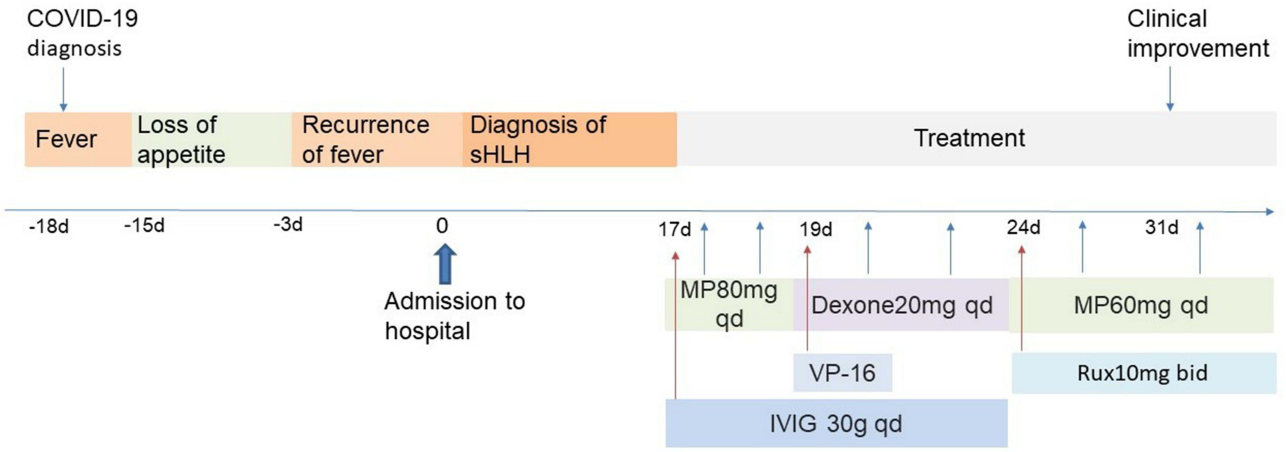

Figure 3 Timeline of the clinical course of the patient.
Abbreviations: MP, methylprednisolone; VP-16, etoposide; IVIG, intravenous immunoglobulin; Rux, ruxolitinib.

ruxolitinib but the progression of sHLH, as the blood cell count increased quickly. The clinical course of this patient is shown in Figure 3.

Discussion

This case describes an elderly HLH secondary to SARS-Cov-2 infection. Ruxolitinib achieved a satisfactory therapeutic effect, including resolution of fever and cognitive function, recovery of cytopenia and hypofibrinogenemia. This case suggested that ruxolitinib may be an alternative therapy for HLH secondary to SARS-Cov-2 infection.

The diagnosis process is relatively tortuous due to the atypical manifestation initially. After excluding other potential causes, HLH secondary to SARS-Cov-2 infection was identified and we initiated treatment as soon as possible to restrain the outbreak of the inflammatory factor storm. For this older patient, it was necessary to exclude infection triggered by other pathogens and tumors. EBV-DNA was low titer positive in peripheral blood lymphocytes in this patient. However, the tests in both peripheral blood lymphocytes and plasma were monitored twice a week after hospitalization. EBV-DNA in plasma was continuously negative, while no significant change was observed in peripheral blood lymphocytes, indicating that HLH was not related to EBV infection. No evidence of tumor was found through detailed examination. In addition, this patient was suspected to have systemic lupus erythematosus (SLE) initially, due to persistent fever, progressive reduction of blood cells, positive antinuclear antibody and anti-dsDNA antibody. New-onset autoantibodies can be detected after SARS-CoV-2 infection in a significant proportion of hospitalized COVID-19 patients.[7] It has been reported that SLE was newly diagnosed after SARS-CoV-2 infection.[8] However, atypical clinical manifestations of multi-system involvement and the poor response to high-dose glucocorticoids did not support the diagnosis of SLE.

HLH is a severe and potentially fatal disease. HLH mortality remains high in adults, ranging from 20% to 88%.[9] It is believed that early diagnosis and goal-directed therapy can improve outcomes. Diagnosis of HLH relies on clinical and laboratory findings. Main symptoms and signs of HLH are fever, potential bleeding tendency and splenomegaly. Other signs including hepatomegaly, lymphadenopathy, rash, and neurological signs are also common and may progress rapidly.[10] Laboratory findings may present with cytopenia, liver dysfunction, elevated ferritin level and lactate dehydrogenase, hyperbilirubinemia, hypertriglyceridemia and hypofibrinogenemia.[11] The diagnosis of HLH in our patient can be made according to HLH-2004 diagnostic criteria[12] and H-Score. Most recently, H-Score consisting of 9 variables is a well-validated scoring system for the diagnosis of sHLH.[13] It also makes a quick evaluation possible for early screening of sHLH in COVID-19.[14]

Secondary HLH is characterized by systemic inflammation, severe cytokine storms and immune-mediated organ damage.[15] It is recognized as a subtype of the cytokine storm syndrome (CSS).[15] Currently, the pathogenesis of sHLH remains incompletely understood. Viral infection is considered to be a common cause. Coronavirus infection causes the aberrant activation of T-cells, dendritic cells, and macrophages, leading to the overproduction of inflammatory cytokines.[16] Researchers have recognized that the hyperinflammatory condition induced by the SARS-Cov-2 infection is similar to sHLH. Elevated serum levels of multiple cytokines including interleukin (IL)-1β, interferon-γ (IFN-γ) and monocyte chemoattractant protein 1 (MCP-1), as well as IL-4, IL-6, IL-10, tumor necrosis factor (TNF) and sCD25 are observed in patients with SARS-Cov-2 infection,[17,18] which shows as a form of sHLH. The period from the onset of initial respiratory symptoms of infection to development of CSS features usually takes 7–14 days and the increase of serum ferritin level is modest (uncommonly exceeding 2000 ng/mL),[19] which is also consistent with the patient we reported. The clinical courses of sHLH varied among patients. HLH can not only be triggered by severe current SARS-CoV-2 infection, but also occur in patients during recovery from mild symptomatic or asymptomatic Sars-CoV-2 infection.[6] For the patients developing sHLH related to previous SARS-CoV-2 infection, the symptoms may reappear after a symptom-free period and deteriorate rapidly.[5] Similar to our patient, there was a previous reported secondary HLH of SARS-Cov-2 infection with negative results for multiple SARS-Cov-2 nasopharyngeal swabs at the time of CSS. The patient was living in the most affected area by COVID-19 and SARS-Cov-2 immunoglobulins G was found to be positive.[6]

The decision to start HLH-directed treatment depends on clinical judgment and assessment of organ function. In addition to managing the triggered factors, standard therapy involves corticosteroids, typically dexamethasone, cyclosporine A, intrathecal therapy, and etoposide, to suppress excess cytokine production by activated T-cells.[11] More emphasis is being placed on individualized treatment. Considering the vulnerability to organ damage caused by cytokine storm in older adults, we used a reduced dose of etoposide 100 mg/m^2 in our patient. In his poor response to treatment condition, ruxolitinib combined with methylprednisolone were promptly given to this patient. Ruxolitinib inhibits activation of JAK/STAT signaling pathways and blocks the downstream effect of multiple cytokines associated with sHLH, including IFN-γ, IL-6, and TNF.[19,20] Recent studies of ruxolitinib in sHLH patients showed good clinical responses as first-line[21,22] and salvage therapy.[23] Ruxolitinib also gained attention for the treatment of cytokine storm associated with COVID-19.[6] A number of clinical trials to evaluate the efficacy of ruxolitinib in COVID-19-related symptoms are ongoing.[24] The successful control in sHLH of ruxolitinib may stem from its broad cytokine-modulating ability. The cytokine storm seen in the course of severe COVID-19 is also reported to be effectively treated with anakinra, which targets IL-1 alone.[25] Future studies should compare the efficacy

and safety of various immunosuppressive drugs in the treatment of COVID-19 sHLH. For this patient, we chose ruxolitinib as salvage therapy according to the accumulative evidence on sHLH. Common inflammation and infection biomarkers, including CRP, procalcitonin and IL-6, were all negative in this patient, which was different from classical HLH. We did not measure the other cytokines and used serum ferritin for tracking treatment response.

Although some researchers have showed the potential effectiveness of ruxolitinib as a first-line treatment for secondary HLH, the efficacy and safety of ruxolitinib in HLH patients secondary to SARS-Cov-2 infection remain to be investigated. More studies are required to explore the application condition, the dosage and duration of the drug therapy.

Conclusion

In conclusion, the diagnosis of sHLH is challenging. We should be aware of the possibility of HLH in mild SARS-CoV-2 infection. Ruxolitinib is a potential choice for COVID-19-related HLH.

Data Sharing Statement

All relevant data has been presented in the manuscript and further inquiry can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This work is in accordance with the Declaration of Helsinki. Institutional approval was not required to publish the case details.

Consent for Publication

Written informed consent has been provided by the patient to have the case details and accompanying images published.

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Disclosure

The authors declare that they have no competing interests in this work.

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