Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) *2023 24(12):1159-1164*
www.jzus.zju.edu.cn; www.springer.com/journal/11585
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https://doi.org/10.1631/jzus.B2300232

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Typical hemophagocytic syndrome associated with cytomegalovirus infection in an immunocompetent patient: a case report and literature review

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Cytomegalovirus (CMV) infection is currently prevalent in populations throughout the world, and 56%–94% of the global population is seropositive for CMV. CMV infection mainly affects immunocompromised hosts. In these cases, it can cause significant symptoms, tissue-invasive disease, and many sequelae including death (Dioverti and Razonable, 2016). The vast majority of healthy adults with CMV infection experience an asymptomatic course; when symptomatic, it manifests as a mononucleosis-like syndrome in approximately 10% of patients (Sridhar et al., 2018). The gastrointestinal tract and central nervous system appear to be the most frequent sites of severe CMV infection in immunocompetent individuals (Rafailidis et al., 2008). However, CMV infection is relatively rarely recorded in immunocompetent hosts.

Here, we describe a case of hemophagocytic syndrome-associated with CMV (HLH-CMV) infection in a 44-year-old woman without known underlying immunodeficiency, who was successfully treated with ruxolitinib. The goal of this paper is to emphasize the importance of early administration of ruxolitinib in immunocompetent patients with HLH-CMV, which can profoundly improve outcomes.

A 44-year-old woman was admitted to our institution (the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China) with a 2-month history of rash and fatigue and a 1-month history of fever and jaundice. The patient complained of severe yellow urine without blurred vision, photophobia, a dry cough, or shortness of breath. She had been healthy in the past, without a history of travel or tick bites. The patient was a worker who abstained from tobacco, alcohol, and illicit drug use.

Approximately two months prior to becoming ill, she experienced a wheal-like rash with an itching sensation on the back, hands, and the back of the thighs without treatment.

One month before admission, the patient noticed that her urine had taken on a severe yellow appearance. Clinicians at the neighborhood hospital found that her total bilirubin level was 32.8 μmol/L, alanine aminotransferase level was 623 U/L, glutamyl transpeptidase level was 249 U/L, and aspartate aminotransferase level was 264 U/L. Liver protection and jaundice relief were administered for two weeks, which was ineffective. During hospitalization in the neighborhood hospital, she developed intermittent fever and a dry cough. A computed tomography (CT) scan of the chest and an electrocardiogram were negative. Ceftizoxime and levofloxacin were administered as anti-infective medications, but the results were unsatisfactory. After that, a large rash appeared on her back. The rash was successfully treated with an antiallergic medication (cetirizine), but the fever persisted. After fresh dark-red granular papules appeared on both sides of her neck, the patient was sent to our hospital for further treatment.

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Received Apr. 10, 2023; Revision accepted Sept. 5, 2023;
Crosschecked Nov. 9, 2023

On the day of admission to our hospital (Day 1), the patient's condition was closely monitored. There was a sharp decrease in the hemoglobin of 80 g/L and platelet count of 71×10^9 L^{-1} (Fig. 1). Her total protein and albumin levels were below normal limits, and serum total bilirubin and direct bilirubin levels were far beyond the normal range. Moreover, her coagulation parameters and liver enzymes were highly abnormal.

Subsequently, we administered empirical hepatocyte protection treatment with acetylcysteine (4 g every 12 h), magnesium isoglycyrrhizinate (0.2 g once daily), adenosylmethionine (1.0 g once daily), and ursodeoxycholic acid (0.25 g three times daily). Given the likely pathogen infection, we commenced meropenem treatment (1 g every 8 h).

Laboratory studies were performed at the time of hospitalization, and the results were summarized in Table 1. They revealed a rapidly progressive pancytopenia, with a maximum decrease of hemoglobin to 40 g/L, platelet count of 30×10^9 L^{-1}, and neutrophil count of 1.14×10^9 L^{-1} after 72 h. Furthermore, levels of ferritin and cytokines interleukin-6 (IL-6) and IL-10 were significantly elevated.

The color doppler ultrasound examination (Fig. 2a) showed that the spleen was enlarged, with a thickness of about 5.2 cm, and the echogenicity of the liver parenchyma was altered. The positron emission tomography (PET)/CT test revealed that liver and spleen were enlarged, and the maximum ^{18}F-fluorodeoxyglucose (FDG) standardized uptake values (SUVs) of the liver and spleen were approximately 4.0 and 3.3 kBq/(mL·MBq·kg), respectively.

Multiple blood and bone marrow cultures were negative for bacteria. A T-cell spot test for tuberculosis infection in whole blood and a *Cryptococcus neoformans* antigen test in serum were negative. Pathogen metagenomic sequencing of peripheral blood samples detected human β-herpesvirus 5 (CMV; 13 182 copies). Tests for CMV immunoglobulin G (IgG) antibodies were positive and CMV IgM antibodies were negative; however, the CMV polymerase chain reaction (PCR) result in blood was 1.58×10^5 copies/mL, implying CMV reactivation. Tests to detect other active viral infections produced the following results: PCR results for parvovirus, Epstein-Barr virus (EBV), and hepatitis B virus (HBV) in blood samples were negative, and tests for treponema pallidum antibody, EBV IgM antibodies, hepatitis B surface antigen (HBs-Ag), hepatitis B e-antigen (HBe-Ag), anti-HBe, anti-hepatitis C, anti-hepatitis D, and anti-hepatitis E were negative, while the tests for EBV IgG antibodies, anti-HBs, and hepatitis B core antibodies (HBcAb) were positive, indicating past HBV and EBV infection. A human immunodeficiency virus antigen–antibody combination assay was negative.

Considering the presence of CMV infection, we commenced treatment with ganciclovir (0.3 g every 12 h).

Further immunological assessments were normal, including anti-liver–kidney microsomal antibodies, anti-nuclear antibodies, antineutrophil cytoplasmic antibodies, anti-cardiolipin antibodies, anti-cyclic citrullinated peptide antibody, and rheumatoid factor.

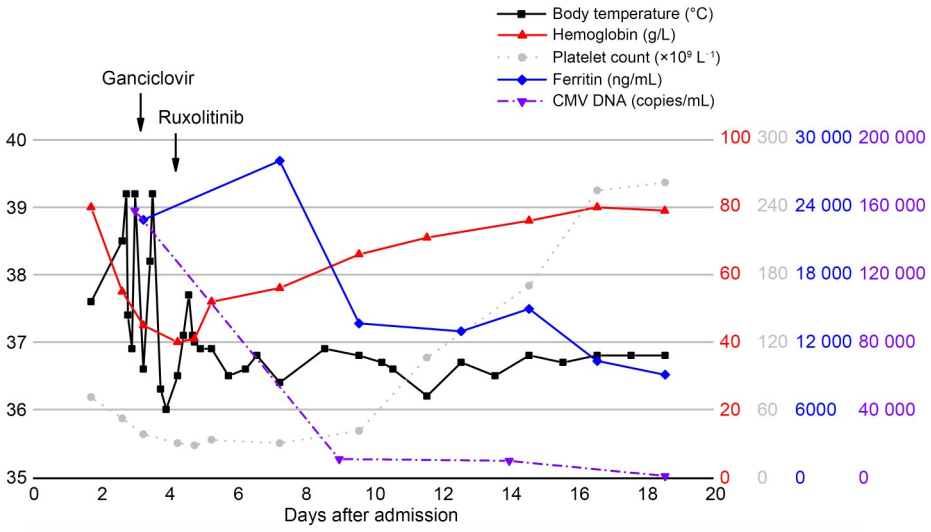

Fig. 1 Chart showing the clinical course after admission. CMV: cytomegalovirus.

Table 1 Results of basic laboratory investigations during hospitalization

Time point	White blood cell count ($\times10^9$ L^{-1})	Neutrocyte count ($\times10^9$ L^{-1})	Lymphocyte count ($\times10^9$ L^{-1})	Red blood cell count ($\times10^{12}$ L^{-1})	Hemoglobin (g/L)	Platelet count ($\times10^9$ L^{-1})	Total protein (g/L)	Albumin (g/L)	AST (U/L)	ALT (U/L)	GGT (U/L)
Day 1	4.80	4.07	0.51	2.90	80	71	48.3	31.6	75	110	197
Day 2	3.30	2.25	0.74	2.01	55	52			44		
Day 3	2.88	1.86	0.61	1.60	45	38	44.3	27.3	61	75	154
Day 4	1.87	1.14	0.48	1.40	40	30	42.2	23.4	44	56	113
Day 5	3.00	1.92	0.70	1.81	52	33	44.3	24.8	38	47	98
Day 18	6.03	5.19	0.56	2.50	79	262	51.8	32.7	14	33	89
Standard value	4.00–10.00	2.00–7.00	0.80–4.00	3.68–5.13	113–151	101–320	65.0–85.0	40.0–55.0	13–35	7–40	7–45

Time point	Soluble CD25 (pg/mL)	Triglyceride (mmol/L)	Total bilirubin (μmol/L)	Direct bilirubin (μmol/L)	LD (U/L)	Fibrinogen (g/L)	D-Dimer (μg/L FEU)	Ferritin (ng/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	CRP (mg/L)
Day 1			184.1	149.9	166	2.01	1493				15.82
Day 2					1518						8.67
Day 3		2.87	153.7	125.9		1.48	1932	222 877.70	112.97	270.95	
Day 4	27 519	1.84	93.7	79.8	1803	1.61	1539				21.72
Day 5		2.00	78.9	70.1	1638	1.12	1050				9.50
Day 18	3449	1.57	23.6	20.0	382	0.90	370	9096.59	3.60	3.68	0.20
Standard value	<6400	0.30–1.70	0.0–21.0	0.0–8.0	120–250	2.00–4.00	0–700	7.00–222.00	0.00–5.30	0.00–4.91	0.00–8.00

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ glutamyl transferase; CD25: cluster of differentiation 25; LD: lactate dehydrogenase; FEU: fibrinogen equivalent unit; IL-6: interleukin-6; CRP: C-reactive protein.

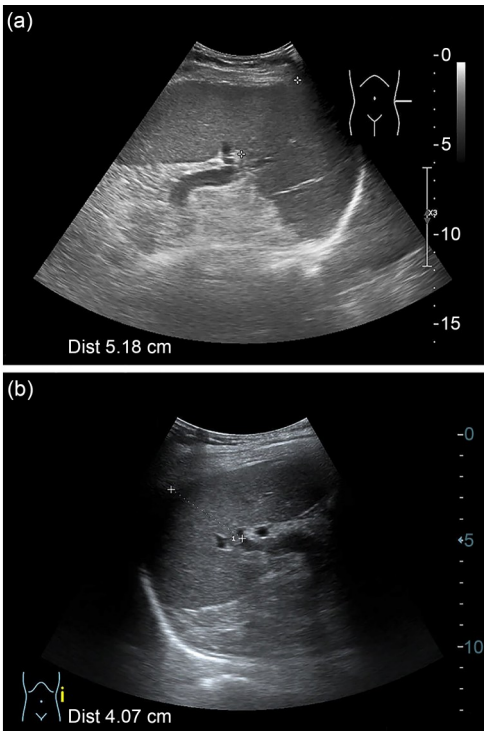

Fig. 2 Colour Doppler ultrasound examination of the abdomen. (a) Ultrasound examination on admission shows splenomegaly, with a thickness of about 5.18 cm. (b) Thickness of spleen after discharge was 4.07 cm. Dist: distance.

A bone marrow aspirate and biopsy revealed trilineage hematopoiesis with active hyperplasia in the myeloid series (mostly myelocyte and metamyelocyte), as well as significantly reduced hyperplasia in the erythroid series (especially erythroblast). There was intense histiocytic proliferation and hemophagocytosis of bone marrow elements (Fig. 3a). The direct and indirect anti-human globulin tests were both negative. Whole-exome sequencing showed no signs of familial hemophagocytic syndrome or relevant immunodeficiency that could cause blood-system abnormalities. Both immunoglobulin heavy chain and T-cell receptor gene rearrangement sequencing in the bone marrow were negative. There was no immunophenotypic evidence of a lymphoproliferative disease in the marrow, as known by flow cytometric analysis. The flow cytometric analysis of the whole blood showed normal expression of signaling lymphocyte activation molecule-associated protein and X-linked inhibitor of apoptosis by natural killer (NK) and cluster of differentiation 8-positive ($CD8^+$) T cells. Soluble CD25 (soluble IL-2 receptor) in whole blood was of 27 519 pg/mL, and the activity of NK cells in whole blood was reduced.

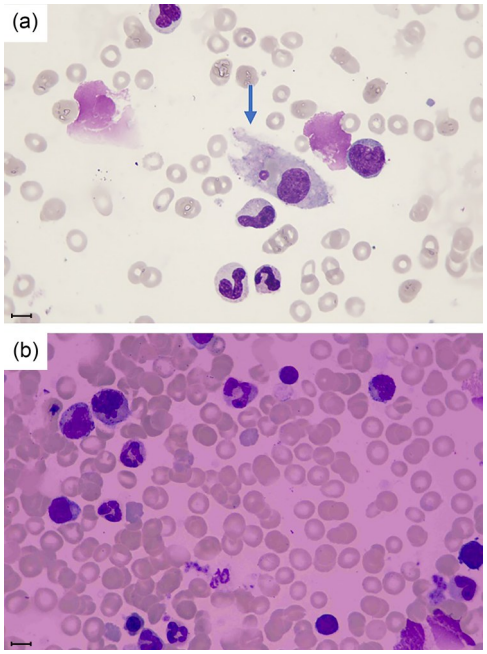

Fig. 3 Pathological results with evidence of hemophagocytosis. (a) Hematoxylin-eosin staining of bone marrow sample on Day 3 showing rare phagocytic cells with engulfed hematopoietic elements (blue arrow). (b) Bone marrow after discharge was normal. The total magnification is 1000×.

Given these results, we considered a diagnosis of HLH-CMV with hepatitis.

Since the patient's condition was constantly deteriorating, on Day 4 we commenced immunoglobulin (20 g, once daily) and ruxolitinib (15 mg, twice daily) combined with methylprednisolone (40 mg, twice daily) for hemophagocytic syndrome, and piperacillin–tazobactam (2.5g, every 12 h) as a preventive anti-infective treatment.

After 18 d of therapy, the patient became afebrile, with evident resolution of her hepatitis and cytopenia (Table 1), leading to her discharge from our hospital on Day 18. After discharge, she continued to take ruxolitinib (15 mg, twice daily) for six weeks and methylprednisolone. The dose of methylprednisolone was 20 mg twice daily from Day 18 to 32, reduced to 10 mg twice daily on Day 33, and then gradually reduced to 4 mg three times daily on Day 44. Finally, on Day 60, she stopped taking all the medications.

At a 2-month follow-up after discharge, she remained well, and her hemoglobin, leucocyte, and platelet levels were nearly normal. Spleen and bone marrow hematopoietic tissue returned to normal (Figs. 2b and 3b). Furthermore, we made a phone visit at seven months following termination of medication, and she said she had no symptoms such as fever, rash, or jaundice.

HLH is a rare and fatal condition caused by the unchecked activation and proliferation of numerous macrophages, NK cells, T lymphocytes, and cytokines (Sepulveda and de Saint Basile, 2017). Although viruses are the most frequent triggers, the proportion of cases caused by CMV is small, especially in immunocompetent hosts.

Only a few other cases of HLH-CMV in immunocompetent adults have previously been reported (Table S1). They described 13 patients ranging from 18 to 72 years of age. All the patients experienced fever, splenomegaly, and slight bi/pancytopenia, except for one case with anemia only. Pneumonia was the main manifestation, and was present in five patients (38.5%), two of whom eventually died. Other symptoms included lymphadenopathy (15.4%), jaundice (15.4%), joint pain (15.4%), and rash (23.1%). All the patients had been treated for HLH-CMV with ganciclovir (84.6%), steroids (53.8%), cytotoxic chemotherapy (30.8%), and immunoglobulin (15.3%). Interestingly, compared to them, our patient did not have pneumonia, and the main clinical manifestations were hepatitis and progressive pancytopenia. Furthermore, successful treatment with ruxolitinib significantly shortened the length of her hospitalization.

Ruxotinib is a selective inhibitor of Janus kinase 1 (JAK1) and JAK2, which ameliorates cytokine-dependent immunopathology in inflammatory disorders by blocking signal transducer and activator of transcription 1 (STAT1) phosphorylation (Das et al., 2016). In the recent years, JAK inhibitors have shown promise for curing related inflammation, cancer, and immune and hematopoietic diseases (Wang et al., 2021; Gao et al., 2022). Ruxotinib is clinically used for the treatment of myelofibrosis (MF) and polycythemia vera (PV), as well as steroid-refractory graft-versus-host disease (GVHD) (Harrison et al., 2012; Vannucchi, 2015; Risitano and Peffault de Latour, 2020). Although ruxotinib is not recommended for the treatment of hemophagocytic syndrome according to the HLH-94 and HLH-2004 protocols, there are a growing number of publications describing its successful use in the treatment of hemophagocytic syndrome. Keenan et al. (2021) conducted a systematic review of 115 publications describing the use of ruxolitinib in patients with HLH. It was incorporated as

part of a salvage regimen in most patients, which was generally effective and well tolerated. Recently, ruxolitinib was used to successfully treat two cases of HLH-CMV in immunosuppressive patients, one of whom had undergone a liver transplant, while the other had interstitial pneumonia. Both received immunosuppressive treatment (Meng et al., 2021; He et al., 2022). However, this is the first publication about ruxolitinib being used in immunocompetent hosts with HLH-CMV.

Although 13 cases of HLH-CMV in immunocompetent people have been studied (Table S1), the majority of whom were treated with ganciclovir and steroids, none was treated with ruxolitinib. Meanwhile, two of the 13 patients were in severe condition with worsening pneumonia. They eventually died in spite of all the measures taken, including immunosuppressive treatment with etoposide and broad-spectrum antibiotics and ganciclovir for CMV. What is noteworthy is that our patient was in the same critical situation, but she received an earlier diagnosis and more timely treatment including ruxotinib for HLH and ganciclovir for CMV, which enabled her to recover to full health within two weeks.

Interestingly, the application of ruxotinib in our patient was safe and effective. Several opportunistic infections have been reported in patients receiving ruxolitinib, including CMV retinitis, reactivation of herpes simplex virus, HBV (Shen et al., 2014; Tong et al., 2014), and tuberculosis (Chen et al., 2015). There is increasing evidence suggesting that ruxolitinib may exert substantial immunosuppressive activity. In particular, ruxolitinib can affect dendritic cell (DC) function, resulting in impaired $CD4^+$ and $CD8^+$ T-cell priming both in vitro and in vivo (Parampalli Yajnanarayana et al., 2015). Inhibition of JAK1 also down-regulates cytokine production (Heine et al., 2013), which may increase the risk of reactivation of potentially life-threatening opportunistic infections. In our patient, ruxotinib was commenced because her condition had progressively deteriorated within the first 72 h after hospitalization. No side effects or opportunistic infections related to the treatment were documented during hospitalization. Therefore, it seems that it was well tolerated and safe in this patient without known underlying immunodeficiencies.

Our study had several limitations. Firstly, although CMV hepatitis should have been confirmed by a histopathologic assessment, we did not obtain histological evidence through a biopsy in this patient due to the high risk of bleeding complications posed by her extremely low platelet levels. Secondly, we only learned the general condition of the patient during the recent phone visit, and it was regrettable that we were not able to assess CMV DNA levels at seven months after stopping ruxotinib therapy, because she did not come to our institution for re-examination.

In conclusion, this case suggests that CMV infection in the immunocompetent population is not as rare as previously thought and that the diseases caused by CMV infection require more attention. Ruxolitinib appears to be safe and efficient during HLH-CMV infection, with the cautious adjunction of ganciclovir. Although ruxolitinib is not yet widely used clinically, it should be considered as a first-line therapy if the patient is in a critical condition.

Data availability statement

Data sharing is not applicable to this article due to protecting study participant privacy but the data are available from the corresponding author on reasonable request.

Acknowledgments

This work was supported by the National Key Research and Development Program of China (No. 2022YFC2304501).

Author contributions

Jianhua HU provided data. Fangfang GENG drafted the initial manuscript. Fangfang GENG, Meifang YANG, Xuan ZHANG, Hong ZHAO, De ZHOU, and Jianhua HU revised the manuscript and approved the final version. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Fangfang GENG, Meifang YANG, Xuan ZHANG, Hong ZHAO, De ZHOU, and Jianhua HU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. IIT20221226A) and with the Helsinki Declaration of 1975, as revised in 2013. Informed consent was obtained from the subject for being included in the study.

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Supplementary information

Table S1