Case Report

Salvage treatment of ruxolitinib for refractory adenovirus-associated hemophagocytic syndrome post-haploidentical allogeneic stem cell transplantation: a case report

Jian Li[1,2#], Qizi Wu[3#], Xuemei Guo[1,2#], Liucheng Rong[1,2], Yongjun Fang[1,2#]

[1]Department of Hematology and Oncology, Children's Hospital of Nanjing Medical University, Nanjing, China; [2]Key Laboratory of Hematology, Nanjing Medical University, Nanjing, China; [3]Department of Hematology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China

Contributions: (I) Conception and design: Y Fang; (II) Administrative support: Y Fang; (III) Provision of study materials or patients: Y Fang; (IV) Collection and assembly of data: J Li, X Guo, L Rong; (V) Data analysis and interpretation: J Li, Q Wu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yongjun Fang, MD. Department of Hematology and Oncology, Children's Hospital of Nanjing Medical University, Code 72, Guangzhou Road, Nanjing 210008, China; Key Laboratory of Hematology, Nanjing Medical University, Nanjing, China. Email: fyj322@189.cn.

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare complication following hematopoietic stem cell transplantation (HSCT). Currently, there is a lack of consensus recommendations for the treatment of post-transplant HLH. This case report emphasizes the successful utilization of ruxolitinib as a salvage therapy for HLH post-HSCT. The aim is to provide valuable insights into the optimal management of this rare and complex complication.

Case Description: We present a case study of an 11-year-old male patient diagnosed with severe aplastic anemia who received a haploidentical HSCT. On the 86th day post-transplantation, the patient developed recurrent fever, hepatomegaly, hypertriglyceridemia, severe pancytopenia, and elevated levels of inflammatory factors and ferritin. Hemophagocytosis was observed in the bone marrow, and subsequent DNA next-generation sequencing identified adenovirus type C infection, leading to a diagnosis of adenovirus-associated HLH. After unsuccessful treatment attempts with cidofovir, dexamethasone, immunoglobulin, plasmapheresis, and etoposide, ruxolitinib was administered. Remarkably, the patient's clinical symptoms rapidly improved, and his test results gradually normalized with ruxolitinib therapy. The adenovirus viral load became undetectable by the 180th day. With continuous remission, ruxolitinib was discontinued on the 137th day post-transplantation, and a 15-month follow-up examination showed no relapse.

Conclusions: We present a case of adenovirus-related secondary HLH (sHLH) post-HSCT, which was effectively treated with ruxolitinib. Our case highlights the potential of ruxolitinib as a therapeutic option for patients with viral infections and sHLH. Nonetheless, the safety and efficacy of this innovative treatment should be evaluated in forthcoming large-scale clinical trials.

Keywords: Hemophagocytic lymphohistiocytosis (HLH); hematopoietic stem cell transplantation (HSCT); adenovirus; ruxolitinib; case report

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening condition characterized by immunological dysregulation and an overactive immune response. Most cases of HLH are triggered by infections, malignancies, or exacerbations of rheumatologic diseases (1). However, HLH resulting from concurrent viral infections after hematopoietic stem cell transplantation (HSCT) is a relatively rare disease. Moreover, there are no established guidelines for the diagnosis and treatment of post-transplant HLH syndrome. Ruxolitinib, a potent inhibitor of Janus kinase (JAK 1/2), is currently used as both primary therapy and secondary therapy to treat HLH (2,3). Despite the efficacy and tolerability of ruxolitinib in treating secondary hemophagocytic lymphohistiocytosis (sHLH), its effectiveness and safety in patients with HLH post-HSCT remain to be investigated. In this report, we present the case of a boy with adenovirus-associated HLH post-HSCT who was successfully cured through salvage treatment concomitant ruxolitinib treatment and management of the viral infection. We present this case in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-27/rc).

Case presentation

We present a case of severe aplastic anemia in an 11-year-old Asian boy diagnosed in March 2022. The patient underwent a haploidentical HSCT from his father as the donor. A concise summary of the patient's clinical information, treatment, and prognosis is provided in *Table 1*. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the parents of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. The conditioning regimen included fludarabine (30 mg/kg/day from day −11 to day −7), busulfan (3.2 mg/kg/day from day −9 to day −7) + cyclophosphamide (60 mg/kg/day from day −6 to day −5), and rabbit antihuman thymocyte globulin (2.5 mg/kg/day from day −4 to day −2). The patient received 3.87×10^6 $CD34^+$ cells and 6.5×10^8 $CD3^+$ cells per kilogram. Graft-versus-host disease (GvHD) prophylaxis consisted of short-term methotrexate (MTX), mycophenolate mofetil (MMF), and cyclosporine. Complete chimerism in peripheral blood was confirmed on day 13 and neutrophil engraftment was confirmed on day 14. On T+16 (16 days after transplantation), the patient developed a persistent fever and rash with pruritus (>50% body surface area), vomiting, and abdominal pain, indicating grade III GvHD. Methylprednisolone, recombinant human c receptor II, and basiliximab were administered, leading to complete improvement of GvHD symptoms. However, cytomegalovirus and Epstein-Barr virus (EBV) activation were detected in peripheral blood on days 43 and 47, respectively. Immunosuppression was reduced, antiviral therapy (ganciclovir 10 mg/kg/day and immunoglobulin 400 mg/kg/day) was administered, and viral regression was evaluated on days 58 and 70. On T+75, the patient experienced frequent urination and acute hematuria, which was diagnosed as hemorrhagic cystitis with positive results for adenovirus and BK virus in the urine specimen polymerase chain reaction (PCR) testing. In terms of patient management, we implemented hydration, analgesia, and administered scopolamine butylbromide and oxybutynin upon the emergence of the initial symptoms. Subsequently, the patient's symptoms gradually improved following these interventions.

On T+86, the patient developed a persistent fever (>39 ℃) along with cytopenia, hyperferritinemia (highest level of 58,325 ng/mL on T+101, with a pre-HSCT level of 1,038 ng/mL), hypertriglyceridemia (4.95 mmol/L), and hypofibrinogenemia (1.7 g/L). Bone marrow aspiration revealed an increased fraction of activated macrophages (*Figure 1A,1B*) and high serum levels of sCD25 (>7,500 pg/mL),

Highlight box

Key findings

- We present a noteworthy case of hematopoietic stem cell transplantation (HSCT) that was complicated by adenoviral infection, subsequently leading to hemophagocytic syndrome. This rare condition was successfully treated using a combination therapy involving ruxolitinib.

What is known and what is new?

- The rare complication of phagocytic syndrome may occur subsequent to HSCT.
- Our case highlights the potential of ruxolitinib as a therapeutic option for patients with viral infections and secondary hemophagocytic lymphohistiocytosis (sHLH).

What is the implication, and what should change now?

- The safety and efficacy of ruxolitinib treatment in sHLH should be evaluated in future large-scale clinical trials.

Table 1 Summary of relevant information, treatment, and prognosis of this case of hematopoietic stem cell transplantation

Age/sex	Primary diagnosis	Conditioning regimen	Type of donor/ graft (HLA match)	GvHD prophylaxis	Neutrophil engraftment	Day of onset or diagnosis of HLH	Treatment	Outcome
11 years/ male	SAA	Bu/Cy + Flu + ATG	Haploidentical PB (father)	CsA/MTX	+14	+86	Dex/VP-16/ IVIg/cidofovir	Improved

SAA, severe aplastic anemia; Bu/Cy + Flu + ATG, busulfan + cyclophosphamide + fludarabine + antihuman thymocyte globulin; HLA, human leukocyte antigen; PB, peripheral blood; GvHD, graft-versus-host disease; CsA/MTX, cyclosporine/methotrexate; HLH, hemophagocytic lymphohistiocytosis; Dex, dexamethasone; IVIg, intravenous immunoglobulin.

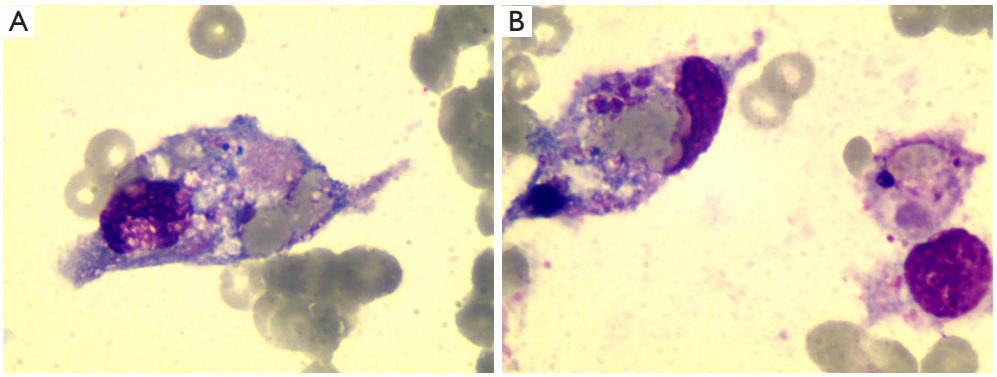

Figure 1 Activated macrophages were observed in the bone marrow at day 104 (Wright-Giemsa stain, ×400). (A) The bone marrow cell morphology showed activated macrophages exhibiting hemophagocytosis in the bone marrow. (B) Activated macrophages that exhibited hemophagocytosis in the bone marrow.

suggestive of HLH. Next-generation sequencing of peripheral blood confirmed adenovirus type C infection (*Figure 2A,2B*). The patient received cidofovir antiviral therapy (5 mg/kg/ week for two doses, then 5 mg/kg/2 weeks for three doses), dexamethasone pulse therapy (10 mg/m^2/day), and etoposide (100 mg/m^2/week for three doses) (*Figure 3A*). However, his fever persisted, leading to transfer to the ICU for plasma exchange and filtration therapy. After undergoing plasmapheresis, there has been a temporary decrease in the patient's levels of inflammatory factors; however, fever remained unstable. Ruxolitinib (5 mg/day) was initiated on +113 days, resulting in the stabilization of body temperature and a decrease in inflammatory cytokine levels, such as sCD25, interleukin-6 (IL-6), IL-10, TNF-α, and serum ferritin (*Figure 3B-3F*). The patient responded well to treatment, achieving negative adenovirus viral load by day 181 and no recurrence observed after fifteen months of hospital discharge.

Discussion

In this report, we utilized ruxolitinib to treat a child with refractory HLH associated with HSCT. Patients who have viral infections induced by immunodeficiency or who are taking immunosuppressants for GvHD are at risk of developing HLH following HSCT. However, HLH is a rare occurrence in the context of HSCT. Diagnosing post-HSCT HLH can be difficult because it presents clinicians with various manifestations that can be confused with other conditions such as capillary leak syndrome, cytokine release syndrome (CRS), engraftment syndrome (ES), infections, systemic inflammatory response syndrome (SIRS)/sepsis, sinusoidal obstruction syndrome (SOS), and thrombotic microangiopathy (TMA) (4). Furthermore, some of these conditions can occur at the same time as post-HSCT HLH. Ferritin levels in HSCT recipients do not strongly correlate with GvHD, making them a potential biomarker to differentiate it from sHLH (5). In our case, the patient's clinical manifestation fulfilled the 2004 classification criteria for familial HLH (fHLH), and his serum ferritin level exceeded 50,000 ng/mL at a certain juncture. Therefore, it is reasonable to presume that he experienced a complication of phagocytic syndrome rather than GvHD.

The first case of HLH following allogeneic HSCT was

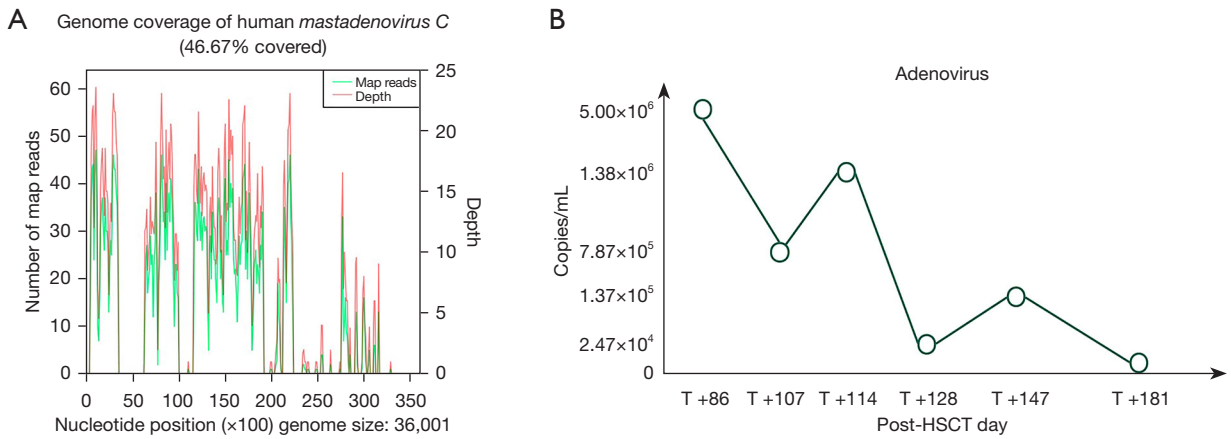

Figure 2 Presents data pertaining to the patient's adenovirus infection. (A) The genome coverage map of human adenovirus type C. The horizontal axis represents the reference genome intervals of human adenovirus type C, with each interval representing 100 base pairs. The coverage of human adenovirus type C in this sample is 46.67%. The primary vertical axis on the left represents the number of sequencing reads, while the secondary vertical axis on the right represents the average sequencing depth, indicating the average number of times each base is sequenced. Green denotes the number of sequencing reads within the intervals, and red denotes the average sequencing depth within the intervals. (B) The real-time quantitative monitoring results of adenovirus in patients eventually achieved successful conversion to negative. HSCT, hematopoietic stem cell transplantation.

documented by Reardon *et al.* (6). A study conducted in Tunisia investigated pediatric and adult cases of sHLH after HSCT, revealing an overall incidence rate of 4%, which increased to 8.8% when focusing solely on allogeneic patients (7). Jaiswal *et al.* recently reported that sHLH occurred in 12.2% of haploidentical peripheral-blood HSCT recipients who received post-cyclophosphamide (PTCY) as prophylaxis against GvHD, with a median onset time of 18 days after transplantation (8).

HLH developing after HSCT consists of 2 types: early and late-onset. The late-onset type is associated with infection-associated HLH. Adenoviruses are among the more common pathogens that increase the risk of post-transplant hematopoietic syndrome, and several reports have been published on this topic (*Table 2*). However, there is no consensus regarding the treatment. In this case, the patient experienced acute GvHD (grade II–III) shortly after hematopoietic stem-cell transplantation. Active anti-GvHD therapy further compromised the patient's immune system, leading to the activation of cytomegalovirus and EBV, as well as the development of hemorrhagic cystitis. These factors created favorable conditions for subsequent adenovirus infection.

A case report has documented successful treatment of adenovirus-associated hemophagocytic syndrome following HSCT with ribavirin and cidofovir (10,12). However, it is generally known that HLH caused by viral infection does not typically respond to specific antiviral therapy, but rather requires treatment with immunosuppressive agents or immunomodulators (13). In the present case, we promptly initiated antiviral treatment with cidofovir along with glucocorticoids, intravenous immunoglobulin, and etoposide to suppress the immune response, and supplemented this with plasma exchange and filtration support. After undergoing the aforementioned treatments, the patient's condition exhibited temporary improvement; however, his body temperature failed to attain a stable state.

Ruxolitinib, a powerful JAK1/2 inhibitor administered orally, exhibits favorable pharmacokinetic properties. It has received approval from the US Food and Drug Administration (FDA) for the treatment of patients diagnosed with myeloproliferative neoplasms and steroid-refractory GvHD (14-16). Ruxolitinib effectively hampers the activity of both JAK1 and JAK2, which are downstream of IFN-gamma and various other HLH-related cytokines, including IL-2, IL-6, IL-10, IL-12, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Recent literature has showcased the successful implementation of ruxolitinib, a Janus-associated kinase inhibitor, in the management of HLH (17-20). However, its routine usage for sHLH management in the context of transplantation is not yet established. Ono *et al.* recounted the successful treatment

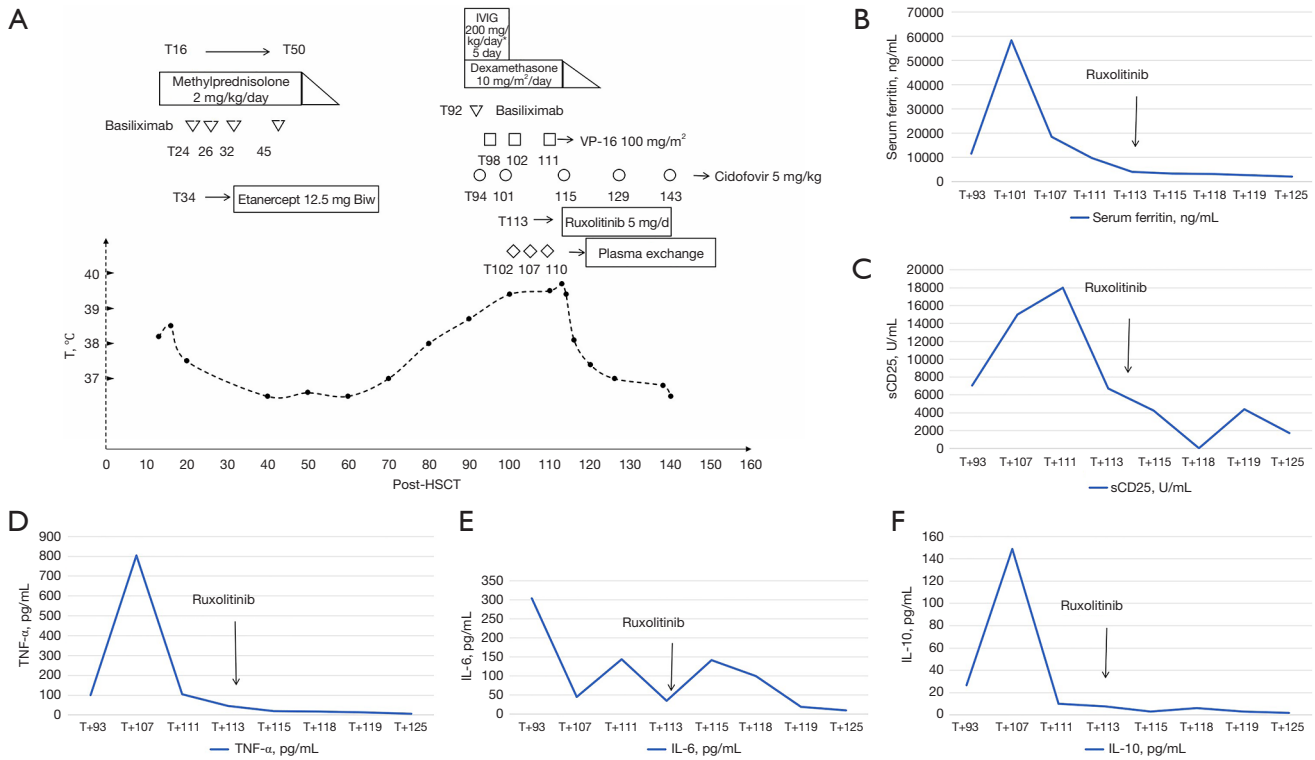

Figure 3 Presents data regarding the treatment history of the patient's complications and the alterations in inflammatory factor levels subsequent to ruxolitinib treatment. (A) The treatment process for complications following patient transplantation. On day 16 post-transplantation, the patient received 2 mg/kg of methylprednisolone for anti-GvHD therapy. On day 24 post-transplantation, the patient was administered basiliximab (10 mg/d +1, +3, +8) and etanercept (12.5 mg biw) for combined anti-GvHD therapy. On day 92 post-transplantation, intensified immunosuppressive therapy was carried out using dexamethasone (10 mg/m^2/d) and immunoglobulin (0.2 g/kg for 5 days). On day 98 post-transplantation, the patient underwent VP-16 chemotherapy (100 mg/m^2 in a total of 3 doses) and received cidofovir (5 mg/kg/week for two doses, then 5 mg/kg/2 weeks for three doses) for antiviral therapy. On day 102 post-transplantation, a plasma exchange procedure was performed. Lastly, on day 113 post-transplantation, ruxolitinib was added at a dose of 5 mg/d. (B-F) Levels of inflammatory factors post-administration of ruxolitinib. HSCT, hematopoietic stem cell transplantation; GvHD, graft-versus-host disease; biw, 2 times a week; TNF-α, tumor necrosis factor-α; IL, interleukin.

of two patients with HSCT-associated HLH employing ruxolitinib (21). Based on the efficacy of ruxolitinib in the management of refractory phagocytic syndrome and corticosteroid-resistant GvHD, it was deemed appropriate to incorporate ruxolitinib into the patient's therapeutic regimen at this juncture of their medical course. On day 113 after the transplantation, following the administration of ruxolitinib (5 mg/d), the patient's body temperature gradually stabilized, and the inflammatory factor test showed a gradual decrease in serum ferritin, sCD25, TNF-α, and IL-6 levels. Ruxolitinib was discontinued on day 137, and there was no recurrence of HLH thereafter.

Serum cytokine profiles are valuable for tracking the progression of HLH. However, these profiles may vary in in cases related to hematopoietic cell transplantation (HCT). In this study, we observed a significant decrease in the levels of inflammatory factors like TNF-α and IL-6 after administering ruxolitinib to the patient under investigation. This finding provides valuable insight into the potential mechanisms underlying the therapeutic effectiveness of ruxolitinib in this specific case. Therefore, monitoring the dynamic changes in various cytokines can aid in evaluating illness activity and therapy response in HLH patients.

One of the limitations of this study was the omission of adenovirus antibody titration prior to patients undergoing HSCT. The inclusion of these data would have provided valuable insights into the patients' baseline immune status.

Table 2 Summary of adenovirus infection-associated HLH cases post-HSCT

Author (years)	Age/sex	Primary diagnosis	Conditioning regimen	Type of donor/ graft (HLA match)	GvHD prophylaxis	Neutrophil engraftment	Day of onset or diagnosis of HLH	Treatment	Outcome
Levy *et al.*, 1990 (9)	6 years/ female	Relapsed Wilm's tumor	Doxorubicin/ local RT/Mel	Autologous BM	–	Primary graft failure	+60	IVIg	Died on T+14 due to graft failure
Reardon *et al.*, 1991 (6)	8 years/ female	ALL (L1) with isolated CNS relapse	Bu/Cy	MRD BM (8/8)	CsA/CS	+10	+38	None	Died on T+42 due to unresolved HLH/ multi-organ failure
Iyama *et al.*, 2005 (10)	51 years/ female	SAA	–	HLA-identical sibling	–	–	–	Oral ribavirin	Improved
Lackner *et al.*, 2008 (11)	9.5 years/ female	AML (M2)	Flu/Mel/ATG	Haploidentical BM (mother, –)	CsA/CS	NR	+24	CS/IVIg/ ribavarin	Alive 2 years after HSCT
Nagamatsu *et al.*, 2021 (12)	65 years/ female	MDS	–	HLA-DRB1 one locus mismatched donor	–	–	+237	Cidofovir + mPSL	Improved

HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; HLA, human leukocyte antigen; GvHD, graft-versus-host disease; RT, radiotherapy; BM, bone marrow; ALL, acute lymphoblastic leukemia; CNS, central nervous system; Bu/Cy, busulfan + cyclophosphamide; MRD, matched related donor; CsA/CS, cyclosporine/corticosteroid; SAA, severe aplastic anemia; AML, acute myeloid leukemia; Flu/Mel/ATG, fludarabine/melphalan/antihuman thymocyte globulin; NR, not report; MDS, myelodysplastic syndrome; mPSL, methylprednisolone; IVIg, intravenous immunoglobulin.

Conclusions

In conclusion, we propose that sHLH should be carefully considered in the evaluation of acutely or chronically unwell allogeneic HSCT recipients who present with an unexplained, culture-negative febrile illness, pancytopenia, or coagulopathy, particularly those with GvHD, EBV infection, or other viral reactivation. Furthermore, ruxolitinib may serve as a viable therapeutic option for individuals with refractory sHLH following HSCT. However, extensive clinical trials are necessary to evaluate the safety and efficacy of this potential treatment.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-27/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-27/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-27/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the parents of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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