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CASE REPORT

Ruxolitinib for Hemophagocytic Lymphohistiocytosis in Multiple Myeloma: Case Report and Review of the Literature

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SUMMARY

Background: **Hemophagocytic lymphohistiocytosis (HLH) is a rare complication of multiple myeloma (MM), with limited data available on its incidence, clinical presentation, and treatment. The underlying mechanisms linking MM and HLH remain unclear, including the potential role of MM treatment agents in triggering HLH.**
Methods: **This case report presents a patient with MM who developed HLH while on lenalidomide maintenance therapy.**
Results: **The patient achieved a successful response to first-line ruxolitinib treatment. While the exact cause of HLH in this case remains unclear, potential factors include the patient's underlying MM, lenalidomide therapy, and recurrent infections.**
Conclusions: **The successful treatment with ruxolitinib highlights its potential as a therapeutic option for HLH in MM patients. Further research is needed to elucidate the pathogenesis of HLH in this context and to optimize treatment strategies.**
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KEYWORDS

Ruxolitinib, hemophagocytic lymphohistiocytosis, multiple myeloma

INTRODUCTION

Multiple myeloma (MM) contributes to less than 1% of the causes of HLH in patients with lymphoproliferative disorders [1]. There is limited data on HLH in MM patients in the literature. All published cases are heterogeneous and differ in terms of diagnosis and treatment protocols. There is limited data on whether MM drugs interfere with the immune system and can therefore also trigger HLH. In this case report, we present the first case of a patient with MM who developed HLH while on lenalidomide maintenance therapy and achieved a response to first-line ruxolitinib treatment.

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CASE

A 69-year-old male with a 2.3-year history of IgG kappa MM (international staging system III, international staging system-revised II), presented with malaise and fever during the 16th course of the lenalidomide maintenance therapy. The patient had been in a stringent complete response after five courses of induction chemotherapy of bortezomib, lenalidomide, and dexamethasone, followed by autologous hematopoietic stem cell transplantation (auto-HSCT) and lenalidomide maintenance therapy. During the initial workup, thrombocytopenia (white blood cell (WBC) count: 6,500/mm^3, hemoglobin level: 12.1 g/dL, platelet count: 55 x 10^9/L), and inflammation (C-reactive protein: 23.2 mg/L) were noted. Lenalidomide was discontinued and sefixime 400 mg/day was initiated due to upper respiratory tract infections. Additionally, intravenous immunoglobulin (IVIG) was administered at a dose of 40 grams (400 mg/kg) due to the patient's recent report of recurrent upper tract respiratory infections. A complete search for a viral infection, including cytomegalovirus, rubella, Epstein-Barr virus, herpes simplex virus, and parvovirus B19, showed that they were noncontributory. Cultures of urine and blood were negative. Due to deepening thrombocytopenia and development of pancytopenia (WBC count: 3,400/mm^3, hemoglobin level: 7.2 g/dL, platelet count: 7 x 10^9/L) on follow-up, the IVIG dose was repeated. A bone marrow aspiration and biopsy were planned for the patient with persistent cytopenia, ongoing need for erythrocyte and platelet replacement, and laboratory findings consistent with complete response to MM. Analysis of the bone marrow aspiration revealed normocellular bone marrow with decreased megakaryocyte number and distribution, along with significant proliferation of phagocytizing macrophages (Figure 1). Considering the persistent pancytopenia, elevated ferritin, and hypertriglyceridemia, the patient was also diagnosed as HLH based on HLH-2004 diagnostic criteria. Due to his poor immune status and anticipating high toxicity to etoposide, ruxolitinib 15 mg twice daily and dexamethasone 10 mg/m^2 daily were initiated [2]. Administration of dexamethasone was rapidly tapered and discontinued due to the development of severe oral mucosal candidiasis on day 15 of ruxolitinib and dexamethasone treatment. The patient's ruxolitinib treatment was completed over a two-month period. At the patient's last follow-up, the blood counts were found to be WBC count 8,300/mm^3, hemoglobin level 10.2 g/dL, and platelet count 225 x 10^9 without requiring further blood transfusions.

DISCUSSION

To our knowledge, this is the first published case of MM accompanied by HLH that responded to first-line ruxolitinib treatment. Although rare in the literature, cases of HLH associated with MM have been reported. A total of 16 case reports have been published describing patients diagnosed with MM who subsequently developed HLH due to various clinical causes (Table 1) [3-18]. The clinical contexts associated with HLH in MM patients were as follows: five cases occurred during MM treatment, three cases after auto-HSCT, two cases at the time of diagnosis, two cases at relapse, two cases due to infection during maintenance MM therapy, and the reason was unknown for the remaining two cases. In our case, the patient had a history of recurrent upper respiratory tract infections and was being followed up while receiving lenalidomide maintenance treatment. While there is limited data suggesting that MM drugs can interfere with the immune system and potentially trigger HLH, lenalidomide is an immunomodulatory drug that can alter T-cell function and exacerbate immune dysregulation. However, there is limited evidence to support a causal relationship between lenalidomide and HLH [16]. Therefore, due to the coexistence of these two conditions and our inability to identify an objective finding, the exact cause of HLH remains unclear. In two reported cases of HLH developing during maintenance MM therapy, infectious agents were identified [15,18]. In the patient receiving Daratumumab-Pomalidomide treatment, E. chaffeensis was identified, while in the patient receiving lenalidomide treatment, EBV was detected. The patient with an E. chaffeensis infection was given high-dose corticosteroids and tocilizumab, while the patient with EBV received HLH-2004 treatment. Unfortunately, neither patient improved, and both patients passed away. Based on this data, we began treatment for this elderly patient with a compromised immune system and a high risk of etoposide side effects using a combination of ruxolitinib and dexamethasone. After developing severe oral mucosal candidiasis due to dexamethasone, the patient received 2 weeks of dexamethasone treatment followed by ruxolitinib alone. One month after starting treatment, the patient became transfusion-independent, and blood counts normalized seven weeks later.

Ruxolitinib, a JAK1/2 inhibitor, is the most studied JAK inhibitor for HLH, in addition to its use in myelofibrosis, graft-versus-host disease, and polycythemia vera. Janus kinase (JAK) proteins, a distinct family of protein tyrosine kinases, are located in the cytoplasm. The JAK pathway activates Signal Transducer and Activator of Transcription (STAT) proteins, leading to a signaling cascade that affects the development, proliferation, and survival of various cell types. The JAK/STAT pathway involves numerous cytokines implicated in HLH. Inhibition of the JAK/STAT axis can inhibit the hyperinflammatory state in HLH and improve disease course. Recent studies have shown that ruxolitinib and ruxolitinib-based therapies are safe and effective treatment options for both first-line and salvage treatment of secondary HLH patients. A retrospective analysis compared the standard HLH-94 protocol to ruxolitinib combined with doxorubicin, etoposide, and dexamethasone (R-DED) in the largest clinical trial evaluating ruxolitinib

Table 1. Treatment for the hemophagocytic lymphohistiocytosis in patients of multiple myeloma.

First author/year	Age/gender	Cause of sHLH	Treatment	Final status for HLH
Prieto E/1986 [3]	NA	NA	NA	NA
Kaito K/1992 [4]	NA	NA	CCS	remission not achieved (dead)
Venizelos ID/2002 [5]	54/F	co-existed at the time of MM diagnosis	VAD	remission
Terrovitis JV/2004 [6]	54/M	after a first course of VAD-T	DEX-E-CyA	remission
Ostronoff M/2006 [7]	54/F	D+16 after auto-HSCT	DEX-High dose IVIG	remission
Machaczka M/2011 [8]	59/M	D+126 after auto-HSCT	CCS-E-IVIG	remission not achieved (dead)
Hsu CM/2019 [9]	59/M	co-existed at the time of aggressive MM relapse	DVR-PACE DVP-PACE DARA-P	remission
Bhatt R/2019 [10]	56/M	co-existed at the time of MM relapse	DEX-E	remission not achieved (dead)
Singh J/2019 [11]	55/F	D+16 after auto-HSCT	DEX-IVIG	remission not achieved (dead)
Mendes FR/2020 [12]	64/M	co-existed at the time of MM diagnosis	pulse CCS DEX-CTX	remission not achieved (dead)
Woods A/2020 [13]	56/M	after a first course of DARA-Pd	DEX-E	remission not achieved (dead)
Runge E/2021 [14]	70/F	during R maintenance	DEX	remission
Mitma AA/2021 [15]	72/M	Ehrlichiosis-related during maintenance DARA-P	pulse CCS-Tocilizumab	remission not achieved (dead)
Milczarek S/2022 [16]	29/NA	under treatment of R with active MM	accordance with HLH-2004 guidelines ISA-Bd	remission (dead)
Constantinescu C/2022 [17]	64/M	under treatment of IRd with active MM	DEX-E	remission not achieved (dead)
Yoshida M/2023 [18]	75/F	EBV-related during maintenance R	HLH-2004 regimen	remission not achieved (dead)

NA - not applicable, CCS - corticosteroid, MM - multiple myeloma, VAD - vincristine/doxorubicin/dexamethasone, VAD-T - VAD/thalidomide, DEX - dexamethasone, E - etoposide, CyA - cyclosporine A, auto-HSCT - autologous hematopoietic stem cell transplantation, IVIG - intravenous immunoglobulin, DVR-PACE - dexamethasone/bortezomib/lenalidomide-cisplatin/doxorubicin/cyclophosphamide/etoposide, DVP-PACE - dexamethasone/bortezomib/pomalidomide - cisplatin/doxorubicin/cyclophosphamide/etoposide, DARA-P - daratumumab-pomalidomide, CTX - cyclophosphamide, DARA-Pd - daratumumab-pomalidomide/dexamethasone, R - lenalidomide, ISA-Bd - isatuximab-pomalidomide/dexamethasone, Ird - ixazomib/lenalidomide/dexamethasone.

for lymphoma-associated HLH. R-DED provided significantly longer survival compared to HLH-94 [19]. These studies and our case suggest that ruxolitinib, and regimens containing it, may be beneficial in the treatment of MM accompanied by HLH.

CONCLUSION

HLH is a rare, rapidly progressive, and life-threatening disorder that is challenging to diagnose. With new treatment options and patient-centered treatment plans, the HLH paradigm is shifting from a universally fatal disease to one with a chance of cure. Ruxolitinib and other JAK/STAT pathway inhibitors show promise for patients with HLH and related immune disorders. More robust data is needed to better define the optimal sequence, dosing, and combinations of JAK inhibitors.

Patient Consent:
Written informed consent was obtained from the patient for publication of this case report.

Declaration of Interest:
The authors declare that they have no known competing financial interests or personal relationships that could

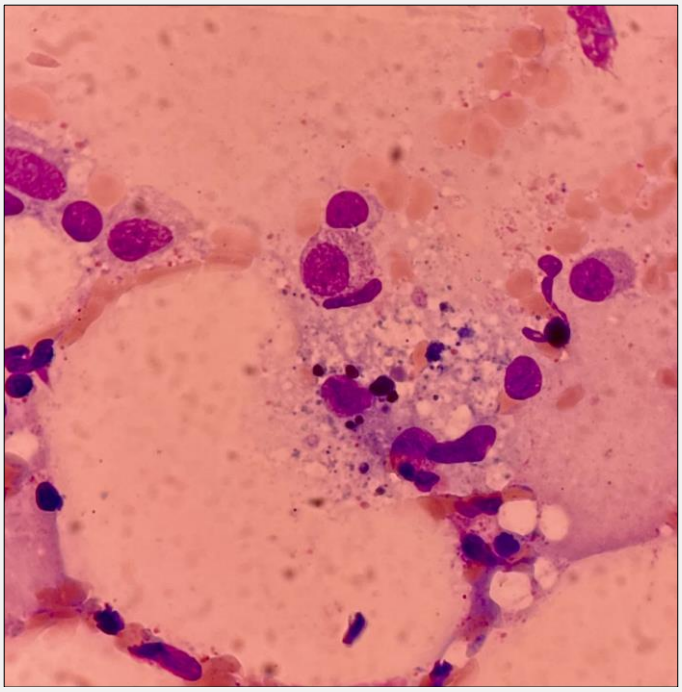

Figure 1. Hemophagocytic lymphohistiocytosis in patient with multiple myeloma.

have appeared to influence the work reported in this paper.
No conflict of interest was declared by the authors.

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