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From Remission to Complication: Hemophagocytic Lymphohistiocytosis and Avascular Necrosis During Brentuximab Therapy in Hodgkin Lymphoma

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Abstract

Relapsed and refractory classical Hodgkin lymphoma (HL) remains a significant clinical challenge despite advances in salvage chemotherapy and autologous stem cell transplantation (ASCT). We report the case of a 37-year-old man diagnosed with stage II classical HL and treated at the university hospital in Alexandria, Egypt, who initially achieved complete remission following doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy but relapsed within six months. He subsequently received salvage dexamethasone, high-dose cytarabine, and cisplatin (DHAP) chemotherapy followed by ASCT, achieving remission.

A second relapse occurred, and the patient was treated with brentuximab vedotin in combination with bendamustine, resulting in complete metabolic remission. During maintenance brentuximab therapy, he developed recurrent low-grade fever, pancytopenia, and progressive left hip pain. Imaging revealed a fluorodeoxyglucose (FDG)-avid osteolytic lesion in the femoral head without evidence of nodal disease, raising concern for relapse.

However, bone marrow biopsy demonstrated hemophagocytosis without lymphoma infiltration. Laboratory evaluation showed markedly elevated ferritin and triglyceride levels, supporting the diagnosis of hemophagocytic lymphohistiocytosis (HLH). Brentuximab therapy was discontinued, and corticosteroids and cyclosporine were administered, followed by gradual clinical and hematologic improvement. Subsequent magnetic resonance imaging (MRI) revealed avascular necrosis of the femoral head with multiple bone infarcts. Follow-up evaluation later confirmed disease relapse.

This case highlights the diagnostic complexity of distinguishing disease progression from treatment-related complications in refractory classical HL and underscores the importance of early recognition of HLH and avascular necrosis as rare but serious adverse events associated with targeted and immunomodulatory therapies. Prompt diagnosis and appropriate management are essential to optimize patient outcomes.

Categories: Hematology, Oncology
Keywords: avascular necrosis, brentuximab vedotin, classical/refractory hodgkin lymphoma, hemophagocytic lymphohistiocytosis, immunotherapy-related complications

Introduction

Hodgkin lymphoma (HL) is a malignant B-cell neoplasm defined by a tumor milieu enriched with inflammatory components. According to GLOBOCAN 2022 estimates, approximately 82,469 new cases of HL and 22,733 deaths occurred worldwide in 2022, corresponding to age-standardized incidence and mortality rates of 0.95 and 0.24 per 100,000 population, respectively. Although first-line treatment achieves long-term survival rates exceeding 85% in high-income countries, outcomes remain less favorable in low- and lower-middle-income regions. In these settings, patients often present at a younger age, with male predominance and more advanced-stage disease [1].

Relapsed or refractory (R/R) classical HL continues to pose a significant therapeutic challenge, particularly in resource-limited environments. In high-income countries, the standard treatment paradigm of salvage chemotherapy followed by high-dose therapy and autologous stem cell transplantation (ASCT) achieves cure rates of approximately 50-60%. Additional improvements have been observed with post-transplant maintenance using brentuximab vedotin (BV) or immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1). In contrast, outcomes in low- and middle-income countries (LMICs) are constrained

by multiple factors and barriers. Notably, only a minority of LMICs possess functional transplant centers capable of managing lymphoma cases effectively [2].

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening, rapidly progressive hyperinflammatory syndrome driven by uncontrolled immune activation. Clinically, it is characterized by persistent fever, cytopenias, organomegaly, biochemical evidence of immune dysregulation, and frequently hemophagocytosis. HLH may arise in the context of genetic susceptibility, malignancies, autoimmune conditions, infections, or drug exposure [3,4].

Drug-induced HLH represents an emerging clinical entity in which systemic hyperinflammation develops following exposure to a causative medication when a medication-related trigger is suspected after evaluation for alternative causes. A recent review identified 39 reported cases, with a median age of 28 years and predominance in males. Anticonvulsants (notably lamotrigine) and antimicrobials (particularly β-lactams) were the most frequently implicated agents. The overall mortality rate was approximately 23%, with worse outcomes observed in older patients and those with underlying hematologic malignancies. These observations highlight the critical importance of early recognition, prompt discontinuation of the offending agent, and timely initiation of corticosteroids with or without HLH-directed immunosuppressive therapy [4,5]. Drug-associated HLH should therefore be considered in the differential diagnosis of fever, cytopenias, and hyperinflammation during cancer treatment, alongside malignancy-associated and infection-associated HLH.

BV, an anti-CD30 antibody-drug conjugate, is widely utilized in the management of classical HL and CD30-positive T-cell lymphomas. Its known adverse effects include peripheral neuropathy, myelosuppression, and cutaneous reactions. Rarely, severe immune-mediated complications such as HLH and cytokine release syndrome (CRS) have been described. Inflammatory complications following BV-containing treatment have previously been reported. Mosalem et al. described severe CRS and an HLH-like syndrome following combined BV and nivolumab; this combination exposure does not establish BV alone as the cause [6].

Herein, we present a case of R/R classical HL with HLH developing during BV therapy. The case highlights a rare presentation and the diagnostic dilemma of distinguishing HLH from infection, lymphoma relapse, and treatment-related myelosuppression. Subsequent osteonecrosis further complicated the distinction between treatment complications, HLH complications, or skeletal lymphoma involvement. This case highlights a possible association between BV exposure and HLH in a patient with relapsed classical HL.

Case Presentation

Initial presentation

A 37-year-old man presented with a one-month history of abdominal pain and intermittent low-grade fever. He was hemodynamically stable on presentation. Physical examination revealed bilateral inguinal lymphadenopathy, while chest and abdominal examinations were otherwise unremarkable. Baseline laboratory investigations were largely within normal limits, except for mildly elevated liver enzymes and lactate dehydrogenase. Contrast-enhanced computed tomography (CT) of the abdomen and pelvis demonstrated multiple enlarged lymph nodes. Consequently, an ultrasound-guided core biopsy of a right inguinal lymph node confirmed classical HL with CD15 and CD30 positivity; the disease was recorded as stage II (Figure *1*) [7,8]. The patient received four cycles of ABVD chemotherapy, with complete metabolic remission documented on positron emission tomography/computed tomography (PET/CT), followed by four further cycles and surveillance [9]. ABVD comprises doxorubicin, bleomycin, vinblastine, and dacarbazine and is typically administered on days 1 and 15 of a 28-day cycle. The patient tolerated nausea, vomiting, fatigue, alopecia, and leukopenia during treatment.

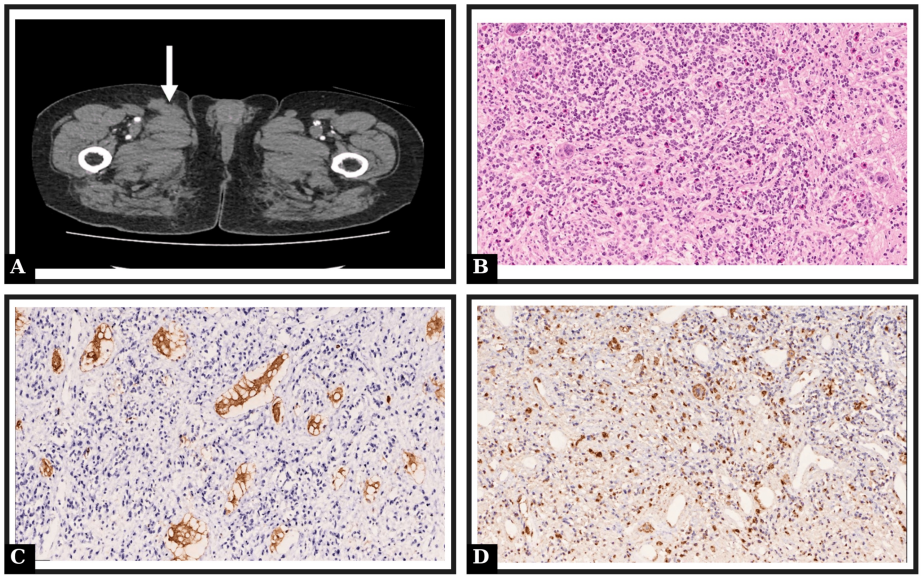


FIGURE 1: Right inguinal lymphadenopathy and histopathologic findings of classical Hodgkin lymphoma

(A) Axial contrast-enhanced CT demonstrating right inguinal lymphadenopathy (white arrow). (B) H&E staining showing scattered large atypical mononuclear and multinucleated cells within a polymorphous inflammatory background. (C) CD30 immunohistochemistry highlighting Hodgkin/Reed-Sternberg cells. (D) CD15 immunohistochemistry demonstrating positivity in Hodgkin/Reed-Sternberg cells.

CT: computed tomography; H&E: hematoxylin and eosin

First relapse

Six months later, PET/CT demonstrated fluorodeoxyglucose (FDG)-avid cervical and pelvic lymphadenopathy, involving nodal regions above and below the diaphragm and consistent with stage III disease. Biopsy of a left submandibular lymph node confirmed recurrent classical HL (Figure *2*). He received six cycles of DHAP chemotherapy, comprising dexamethasone, high-dose cytarabine, and cisplatin, achieving complete metabolic remission documented on PET/CT, followed by ASCT in August 2023 [10].

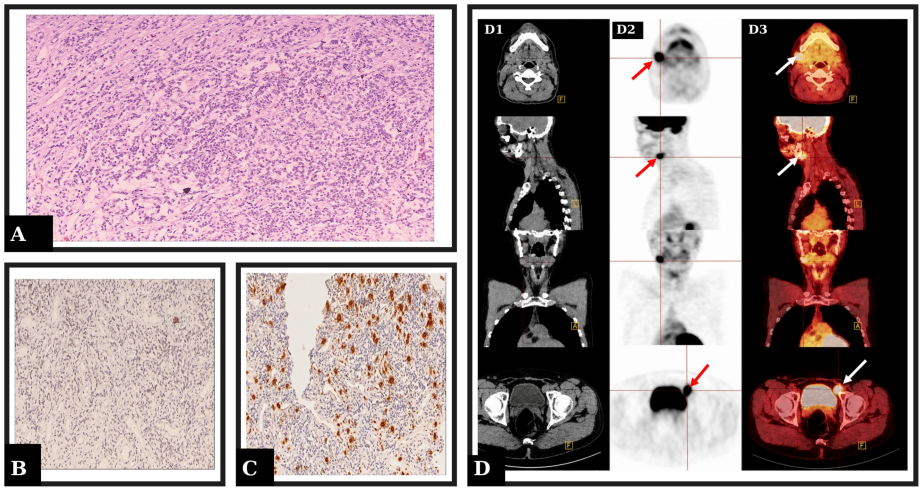


FIGURE 2: Histopathologic confirmation of recurrent classical Hodgkin lymphoma on repeat biopsy and corresponding PET/CT findings

(A) H&E staining showing large atypical mononuclear and binucleated cells with prominent nucleoli, consistent with Hodgkin/Reed-Sternberg cells, within a polymorphous inflammatory background. (B) CD30 immunohistochemistry demonstrating positivity in scattered large atypical cells. (C) CD15 immunohistochemistry demonstrating positivity in scattered large atypical cells. (D) CT (D1), PET (D2), and fused PET/CT (D3) images. Each column includes, from top to bottom, axial neck, sagittal, coronal, and axial pelvic views. Red arrows in D2 and white arrows in D3 highlight FDG-avid cervical and pelvic lymph nodes.

PET/CT: positron emission tomography/computed tomography; H&E: hematoxylin and eosin; FDG: fluorodeoxyglucose

Second relapse

In November 2024, a separate PET/CT demonstrated cervical and pelvic lymphadenopathy, and biopsy confirmed a second relapse. The patient was treated with BV in combination with bendamustine, achieving complete metabolic remission documented on PET/CT after four cycles. Maintenance therapy with BV was subsequently initiated [11]. Figure *2* presents representative images from the first relapse only; subsequent response assessments and relapse investigations were separate PET/CT examinations.

Complications during brentuximab therapy

Approximately one week after each cycle of brentuximab, the patient developed recurrent fever, with a maximum documented temperature of 39°C and generalized bone pain, accompanied by laboratory evidence of pancytopenia and neutropenia. Blood-count recovery generally took one to two weeks, and granulocyte colony-stimulating factor (G-CSF) was used intermittently to support neutrophil recovery before subsequent cycles. Bone marrow examination was performed during the post-treatment cytopenic nadir, approximately one week after BV administration, and demonstrated hemophagocytosis without identified lymphoma infiltration (Figure *3*).

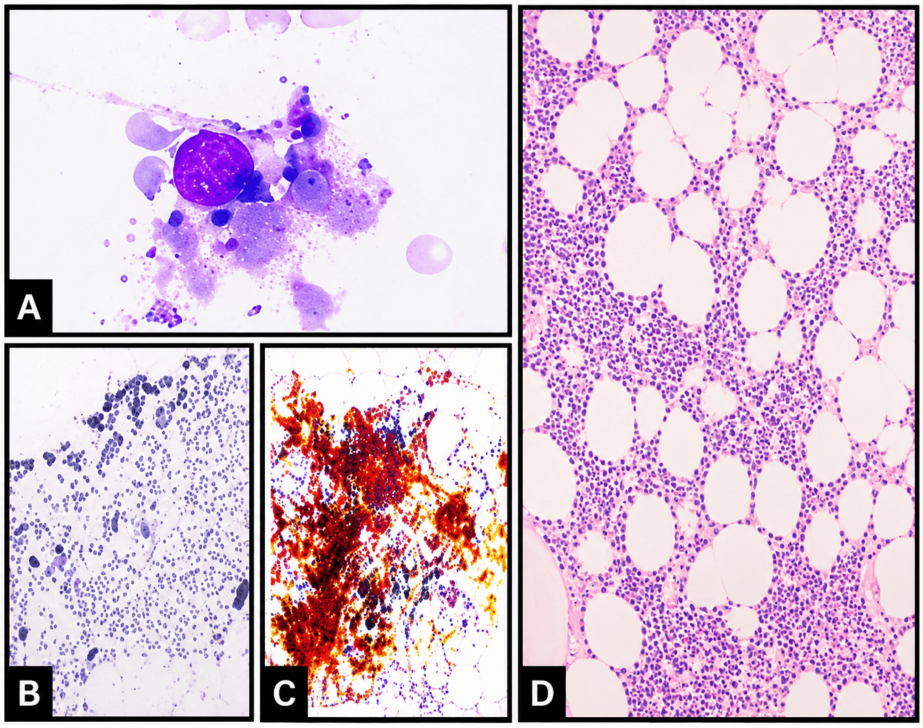


FIGURE 3: Bone marrow morphology demonstrating hemophagocytosis and marked marrow hypocellularity

(A) May-Grünwald-Giemsa-stained bone marrow aspirate showing an activated histiocyte with hemophagocytosis. (B) Romanowsky-stained aspirate demonstrating a markedly hypocellular, hemodiluted marrow with severely reduced hematopoietic elements and no overt malignant infiltrate. (C) Perls' Prussian blue stain showing markedly increased marrow iron stores with coarse hemosiderin deposition. (D) Bone marrow trephine biopsy (hematoxylin and eosin) demonstrating profound hypocellularity with extensive fatty replacement and only small residual hematopoietic islands.

Further evaluation revealed serum ferritin of 4,042 ng/mL, triglycerides of 682 mg/dL, and elevated C-reactive protein (Table *1*). The diagnosis of HLH was supported by the combination of fever, multilineage cytopenias, hyperferritinemia, hypertriglyceridemia, and marrow hemophagocytosis. An HScore of 238 was reported. Testing for the viral markers listed in Table *1* was negative, and no lymphoma infiltration was identified in the sampled marrow. The temporal association with BV raised suspicion of a treatment-associated trigger; however, occult lymphoma activity, infection, and effects of preceding treatment could not be definitively excluded. Brentuximab was discontinued, and the patient was treated with corticosteroids and cyclosporine, resulting in clinical and hematologic improvement.

Parameter	Result	Reference range
Hemoglobin (Hb)	8.5 g/dL	12.0-16.0 g/dL
Platelet count	55×10⁹/L	150-400×10⁹/L
White blood cell count	1.4×10⁹/L	4.0-11.0×10⁹/L
Absolute neutrophil count (ANC)	0.63×10⁹/L	1.5-7.5×10⁹/L
Serum triglycerides	682 mg/dL	<150 mg/dL
Serum fibrinogen	450 mg/dL	200-400 mg/dL
Serum ferritin	4,042 ng/mL	30-400 ng/mL
C-reactive protein (CRP)	23 mg/L	<5 mg/L
Aspartate aminotransferase (AST)	38 U/L	10-40 U/L
Hepatitis B surface antigen (HBsAg)	Negative	Negative
Hepatitis C virus antibody (HCV Ab)	Negative	Negative
Human immunodeficiency virus antibody (HIV Ab)	Negative	Negative
Cytomegalovirus polymerase chain reaction (CMV PCR)	Negative	Negative
Epstein-Barr virus polymerase chain reaction (EBV PCR)	Negative	Negative
Abdominal and pelvic ultrasonography	No organomegaly	-
Clinically	Fever up to 39°C	36.5-37.5°C

TABLE 1: Laboratory findings during evaluation for hemophagocytic lymphohistiocytosis (HLH)

Three months later, the patient developed acute kidney injury, and cyclosporine was discontinued. Additionally, he reported persistent left hip pain. CT imaging revealed an osteolytic lesion in the left femoral head, initially suspicious for lymphoma involvement. PET/CT demonstrated intense FDG uptake involving the left femoral head without associated FDG-avid lymphadenopathy (Figure *4*). MRI demonstrated femoral head osteonecrosis and additional femoral bone infarcts, including a femoral head double-line sign (Figure *4*) [12]. These findings may have been related to cumulative glucocorticoid exposure during previous lymphoma treatment and subsequent HLH therapy, although the contribution of individual treatment courses could not be established. Corticosteroid tapering was initiated.

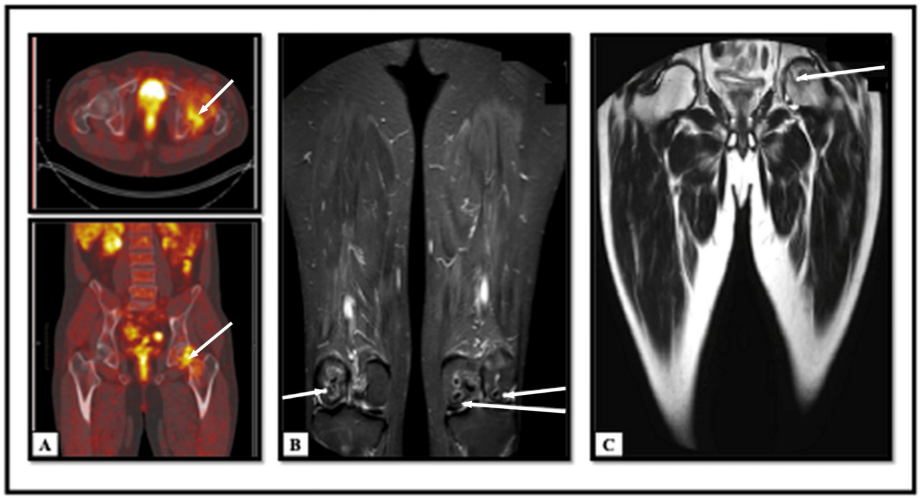


FIGURE 4: MRI demonstrating left femoral head osteonecrosis and additional femoral bone infarcts and PET/CT demonstrating hypermetabolic involvement of the left femoral head

(A) Axial and coronal PET/CT images demonstrating focal increased FDG uptake in the left femoral head, at the site characterized as osteonecrosis on MRI (white arrow). (B) STIR coronal image of both thighs showing bilateral bone infarcts evident as intramedullary altered signal within the femoral condyles associated with hyperintense serpiginous outline (white arrow). (C) T2-weighted coronal image showing marrow edema along with double-line sign with inner hyperintense rim and outer hypointense line at the junction of the normal and ischemic marrow (white arrow). It is considered highly specific for femoral head AVN.

MRI: magnetic resonance imaging; PET/CT: positron emission tomography/computed tomography; FDG: fluorodeoxyglucose; STIR: short tau inversion recovery; AVN: avascular necrosis

Subsequent disease course

Follow-up bone marrow evaluation showed improvement in the previously described histiocytic infiltration, consistent with a response to treatment but not diagnostic of a drug-induced etiology. However, during surveillance, the patient developed new cervical lymphadenopathy, and his scan confirmed disease relapse. The subsequent management was challenging due to the need to discontinue BV because of suspected treatment-associated HLH despite prior complete response, raising concerns for disease control in a relapsed setting with limited alternatives. The patient was therefore transitioned to pembrolizumab in combination with gemcitabine, dexamethasone, and cisplatin (GDP) chemotherapy through a patient support program. The patient achieved complete remission, as confirmed by PET/CT imaging. The clinical timeline is summarized in Figure *5*.

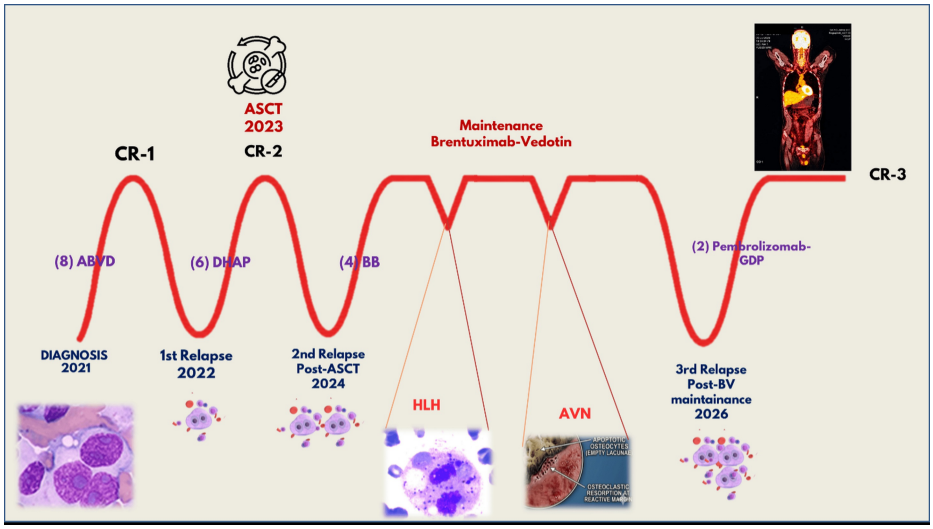


FIGURE 5: Clinical timeline illustrating disease course, relapses, treatments, and major complications

ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; DHAP: dexamethasone, high-dose cytarabine, and cisplatin; BB: bendamustine and brentuximab vedotin; ASCT: autologous stem cell transplantation; BV: brentuximab vedotin; GDP: gemcitabine, dexamethasone, and cisplatin; HLH: hemophagocytic lymphohistiocytosis; AVN: avascular necrosis; CR: complete remission

The figure was created by the authors using PowerPoint (Microsoft Corporation, Redmond, Washington, United States).

Discussion

The management of R/R HL is becoming increasingly complex, particularly in resource-limited settings. While outcomes have improved substantially in high-income countries with the incorporation of high-dose chemotherapy, ASCT, and targeted therapies, these advances are not uniformly accessible worldwide. In such environments, delayed diagnosis, limited access to advanced imaging and transplant facilities, and restricted availability of novel agents may contribute to suboptimal outcomes [13].

In our case, despite initial complete remission and subsequent ASCT, the patient experienced multiple relapses, illustrating the challenge of maintaining disease control through successive lines of therapy. The introduction of targeted therapies, including antibody-drug conjugates and immune checkpoint inhibitors, has transformed the treatment landscape of R/R HL.

BV, in particular, has demonstrated significant efficacy in post-transplant relapse and heavily pretreated patients. Pembrolizumab has also demonstrated activity in this setting; however, KEYNOTE-087 evaluated pembrolizumab monotherapy and does not directly establish the efficacy of pembrolizumab plus GDP [14]. However, access to these therapies remains inconsistent, and prolonged use may be associated with cumulative toxicities [6].

In our patient, BV achieved disease control but was followed by a rare and potentially fatal inflammatory complication, highlighting the delicate balance between therapeutic benefit and toxicity in heavily treated individuals. Persistent cytopenias during HL management represent a diagnostic and therapeutic dilemma. They may arise from disease progression, bone marrow infiltration, infections, or treatment-related toxicity [15].

In this context, the diagnosis of HLH is particularly challenging, as many of its clinical and laboratory features overlap with these conditions [16]. Our patient developed recurrent fever, pancytopenia, and biochemical evidence of hyperinflammation, prompting further evaluation. Bone marrow examination demonstrating hemophagocytosis, along with elevated ferritin and triglyceride levels, supported the diagnosis of HLH. Ferritin elevation alone cannot distinguish HLH from malignancy, infection, or treatment-related inflammation. There is no universal "acceptable" post-chemotherapy ferritin level that establishes an elevation as benign. In this patient, ferritin of 4,042 ng/mL was interpreted alongside fever, cytopenias, marked hypertriglyceridemia, and marrow hemophagocytosis rather than used as an isolated diagnostic finding [3,16].

Drug-induced HLH is increasingly recognized with the expanding use of immunomodulatory therapies.

Although malignancy-associated HLH is more commonly described in lymphoma patients, the temporal relationship between brentuximab administration and symptom onset raised suspicion of a treatment-associated trigger. However, a causal association cannot be confirmed because occult lymphoma activity, infection, and effects of preceding treatment remain plausible alternative contributors. The exact mechanism remains incompletely understood but is thought to involve immune dysregulation and excessive cytokine activation [5]. Importantly, brentuximab has also been associated, albeit rarely, with CRS [17], which shares overlapping clinical features with HLH. The overlapping features of these syndromes require interpretation within the overall clinical context; cytopenias, elevated ferritin, and hemophagocytosis alone do not establish a definitive distinction [18].

Early recognition and prompt management of HLH are essential to prevent progression to multiorgan failure. In this case, discontinuation of brentuximab and initiation of immunosuppressive therapy with corticosteroids and cyclosporine resulted in clinical improvement. However, treatment itself is not without risk. Cyclosporine-associated nephrotoxicity may have contributed to the development of acute kidney injury in our patient, further complicating management and necessitating treatment modification.

Another notable complication in this case was the development of avascular necrosis, which has been increasingly reported in patients with HLH and hematologic malignancies. The pathogenesis of avascular necrosis is multifactorial and is strongly associated with prolonged corticosteroid exposure, microvascular compromise, and underlying inflammatory states. Studies have reported a relatively high prevalence of osteonecrosis among HLH patients, likely reflecting the cumulative effects of high-dose steroid therapy [19]. Our patient received dexamethasone-containing salvage chemotherapy and subsequent corticosteroids for HLH. The contribution of glucocorticoids to osteonecrosis is plausible, but cumulative exposure and a dose-response relationship cannot be assessed confidently without complete treatment records. Imaging findings favored femoral head osteonecrosis and additional bone infarcts over active skeletal lymphoma, underscoring the importance of accurate radiologic interpretation to avoid misclassification as disease progression [19].

Avascular necrosis poses an additional therapeutic challenge, particularly in patients with relapsed lymphoma who require ongoing systemic therapy. Progressive joint damage can significantly impair mobility and performance status, thereby limiting treatment tolerance and influencing therapeutic decision-making. In this context, distinguishing between disease-related skeletal involvement and treatment-related complications is crucial to guide appropriate management strategies [20].

Finally, this case highlights the complexity of managing heavily pretreated HL patients, in whom overlapping disease manifestations and treatment-related toxicities may obscure diagnosis and complicate clinical decision-making. The subsequent relapse and need for further therapy with immune checkpoint inhibitors further underscore the evolving challenges of immunotherapy, including the risk of immune-related adverse events and atypical inflammatory complications, necessitating careful monitoring and individualized treatment strategies.

Conclusions

This case highlights the complexity of managing R/R classical HL, where treatment response may be offset by severe complications such as suspected BV-associated HLH. It underscores the importance of early recognition of treatment-related complications and the challenges of balancing efficacy and safety, particularly in resource-limited settings where access to alternative therapies and advanced supportive care may be constrained. Individualized, multidisciplinary management remains essential to optimize outcomes. The available evidence supports a temporal association rather than proven drug-induced causation. Osteonecrosis may have reflected cumulative glucocorticoid exposure across multiple treatment courses.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Supervision: Mohamed H. Elbahoty, Ashraf Elghandour

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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