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Successful treatment of two cases of classical Hodgkin lymphoma-associated hemophagocytic lymphohistiocytosis with R-CEPP

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Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by an extreme inflammatory response with unrestricted macrophage activation leading to phagocytosis of formed blood elements. HLH occurs as a primary familial disorder in about 25% of cases, characterized by autosomal recessive inheritance of gene mutations that disrupt normal programmed cell death (including *PRF*, *UNC13D*, *STX11*, and *STXBP2*), or as a secondary disorder associated with malignant, infectious or autoimmune processes.[1,2] HLH is diagnosed by molecular genetic testing or by the presence of at least five of eight diagnostic criteria: fever, splenomegaly, cytopenias in two or more lineages (hemoglobin <9 g/dL, platelets <100 × 10⁹/L, or neutrophils <1.0 × 10⁹/L), hypertriglyceridemia (fasting ≥265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL), low or absent NK cell activity, hyperferritinemia (>500 µg/dL), increased soluble interleukin-2 (IL-2) receptor (>2400 U/mL), and evidence of hemophagocytosis in bone marrow, spleen, or lymph nodes.[3]

Lymphoma-associated HLH accounts for the majority of malignancy-associated cases, approximately 25% to 30% of adult HLH cases overall, and is commonly associated with Epstein–Barr Virus (EBV) infection.[4–6] The association of HLH with classical Hodgkin lymphoma (cHL) is uncommon and has only rarely been reported.[5,7–13] Lymphoma-associated HLH is rapidly progressive and often fatal.[5,14] HLH-associated liver dysfunction amplifies the risk of toxicities with standard cHL therapy, and doxorubicin in particular, precluding the use of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). The optimum treatment for cHL-associated HLH is not known. Recently, we successfully treated two cases of cHL-associated HLH with rituximab and

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cyclophosphamide, etoposide, procarbazine, and prednisone (CEPP; cyclophosphamide 600 mg/m² on days 1–8, etoposide 70 mg/m² on days 1–3; procarbazine 60 mg/m² PO, and prednisone 60 mg/m² PO daily on days 1–10), a regimen with activity against EBV, cHL, and HLH that has been safely used in the setting of liver failure.[15,16]

Our first case involved a 31-year-old man who presented with fatigue and neck swelling. Computed tomography (CT) of the neck showed posterior cervical chain lymphadenopathy. Heterophile antibody was positive and he was diagnosed with infectious mononucleosis. He was treated conservatively with rest and analgesics.

Three weeks later, he presented to the emergency department with malaise, nausea, and vomiting. He was febrile, tachycardic, and jaundice. Laboratory evaluation revealed WBC $3.0 \times 10^9/L$, hemoglobin 7.5 g/dL, platelets $122 \times 10^9/L$, creatinine 1.71 mg/dL, LDH 2766 U/L (normal range 100–330 U/L), alkaline phosphatase 254 U/L, AST 271 U/L, ALT 119 U/L, total bilirubin 4.2 mg/dL, and direct bilirubin 2.1 mg/dL. He subsequently developed worsened pancytopenia with WBC $2.7 \times 10^9/L$, ANC $2.4 \times 10^9/L$, hemoglobin 7.0 g/dL, and platelets $29 \times 10^9/L$, hepatic failure with encephalopathy, and renal failure. Over the following week, his total bilirubin increased to 20.7 mg/dL, fibrinogen fell to 85 ng/dL, and ferritin peaked at >33,000 ng/mL (normal range 20–300 ng/mL). Additional workup revealed increased triglycerides (338 mg/dL) and decreased NK cell activity (0.3 NK lytic units measured by chromium release methodology, normal >2.6) consistent with HLH.

HIV screening, hepatitis serologies, and blood cultures were all unrevealing. EBV and CMV serologies were IgG positive and IgM negative, and EBV DNA viral load by quantitative polymerase chain reaction (PCR) was 448,000 copies/mL. CT of the abdomen and pelvis revealed mild hepatosplenomegaly and scattered lymphadenopathy. Excisional biopsy of a neck lymph node showed diffuse infiltrate of large, malignant lymphoid cells including Reed–Sternberg cells. Bone marrow biopsy showed histiocytes, occasional hemophagocytosis, and Reed–Sternberg cells that labeled for CD30, dim PAX5 and were positive for EBV RNA by *in situ* hybridization. With this information, his diagnosis was refined to HLH-associated with clinical stage IVB mixed-cellularity type cHL.

Prior to the diagnosis of cHL, the patient had been treated for presumed HLH with 20 mg of dexamethasone daily for two days and a single dose of etoposide 100 mg/ m² based on the HLH-94 regimen.[16] He also received 375 mg/m² of rituximab for EBV viremia. His liver failure precluded the use of ABVD, so he was treated with CEPP with a 20% dose reduction of cyclophosphamide, etoposide and procarbazine. After one cycle of R-CEPP therapy his fever, splenomegaly, renal failure, and liver failure completely resolved, fibrinogen level normalized, and there was marked improvement of his anemia and thrombocytopenia consistent with resolution of HLH. Furthermore, EBV viral load by polymerase chain reaction (PCR) became undetectable. He went on to receive six cycles of ABVD and obtained a complete cHL remission based on post-treatment imaging with PET/CT and repeat bone marrow examination. He remains clinically and radiographically in remission, now more than one year out from treatment.

Our second case involved a 71-year-old woman with history of IgG kappa plasma cell myeloma that was previously treated with an autograft follow by lenalidomide maintenance (10 mg daily) for nearly six years. She presented with fatigue, back pain, rising monoclonal paraprotein, and worsening anemia. Her bone survey revealed new lytic skeletal lesions. She was started on bortezomib and dexamethasone salvage for her myeloma, but her course deteriorated. By treatment day eight, she developed fever, tachycardia, tachypnea with diffuse crackles in the lungs, and jaundice. Laboratory evaluation showed WBC $7.9 \times 10^9/L$, hemoglobin 7.2 g/dL, platelets $107 \times 10^9/L$, creatinine 1.52 mg/dL, alkaline phosphatase 576 U/L, AST 401 U/L, ALT 394 U/L, total bilirubin 4.3 mg/dL, direct bilirubin 3.0 mg/dL. She was admitted to the hospital and empirically treated for pneumonia with some clinical improvement. Her liver dysfunction was attributed to hepatotoxicity from bortezomib and progression of her myeloma. Over the next week, she developed worsened pancytopenia with WBC $2.7 \times 10^9/L$, ANC $2.3 \times 10^9/L$, hemoglobin 7.0 g/dL, and platelets $21 \times 10^9/L$. Her total bilirubin rose to 7.2 mg/dL and ferritin peaked at 27,066 ng/mL (normal range 20–300 ng/mL). Further workup revealed elevated serum triglycerides (742 mg/dL) and elevated soluble IL-2 receptor (27,046 pg/mL, normal range 45–1105 pg/mL) consistent with HLH.

Hepatitis B core and surface antibodies were positive but surface antigen and blood viral levels were undetectable. EBV viral load in the blood by quantitative PCR was 12,000 copies/mL. CT of the chest, abdomen, and pelvis revealed scattered ground-glass opacities in the lungs, skeletal lytic lesions, and liver lesions suggestive of fibrosis or inflammation. A bone marrow biopsy and aspiration were performed that showed hemophagocytosis and atypical lymphoid cells that expressed CD30, CD15, dim nuclear PAX5, and EBV RNA by *in situ* hybridization consistent with cHL, as well as 15% clonal plasma cells (Figure 1). She was diagnosed with HLH associated with cHL as well as progressive myeloma.

She received 375 mg/m² of rituximab and CEPP for her cHL-associated HLH and EBV viremia with dose reduced cyclophosphamide (50%), etoposide (75%), and procarbazine (50%) for the first cycle. Her HLH promptly resolved with normalization of fevers, cytopenias, and liver function following her first cycle of R-CEPP. Her EBV viral load became undetectable. She subsequently completed six cycles of R-CEPP without dose adjustment and tolerated this well aside from an episode of neutropenic fever. Bone marrow examination at the end of therapy showed normal tri-lineage hematopoiesis with no evidence of cHL, HLH, or clonal increase in clonal plasma cells. CT of the chest, abdomen, and pelvis confirmed a complete radiographic response of cHL.

There are no prospective trials to guide standard treatment for adult HLH. Common approaches for adult HLH have been extrapolated from reports of the use of epipodophyllotoxins alone or in combination with corticosteroids in children with HLH. [17,18] The efficacy of etoposide-based regimens was subsequently validated in the prospective HLH-94 and HLH-2004 trials [3,16]; however, the efficacy and toxicity of these approaches in adult HLH remain unclear and outcomes are generally not as favorable.

Treatment of cHL associated with HLH is complicated by the hepatic and renal dysfunction that are characteristic of HLH. Standard cHL treatments such as ABVD are generally contraindicated with severe liver failure, limiting treatment options in the setting of HLH.

Furthermore, the use of ABVD for cHL-associated HLH is associated with poor outcomes – in four reported cases, one recovered, one relapsed, and two died.[8–10,12] Therefore, the optimal treatment approach for cHL-associated HLH is not known. Notably, CEPP has been shown to be a well-tolerated and effective therapy in non-Hodgkin lymphoma and cHL, even in the setting of marked liver and renal dysfunction.[15,19]

The tolerability of R-CEPP, even in the setting of liver failure, long track record for rituximab in treating EBV infection, activity for cHL, and incorporation of etoposide and corticosteroids make it an attractive option for cHL-associated HLH, but data on safety and efficacy are lacking. Based on the favorable features of R-CEPP, we successfully treated two cases of cHL-associated HLH with very encouraging outcomes. Both patients dramatically improved after R-CEPP treatment with prompt resolution of HLH-associated complications allowing for definitive treatment of the underlying cHL. The first patient remains in remission after six cycles of ABVD-based therapy now more than one year out from completion of treatment. The second, frailer, patient completed six cycles of R-CEPP with excellent tolerance and achieved a complete remission of HLH and cHL as well as an excellent bone marrow response of her underlying myeloma at the end of treatment. Interestingly, the second patient was receiving maintenance lenalidomide after her autograft for myeloma, a treatment that has been associated with secondary malignancies, although cHL-associated HLH has not been previously reported.

The use of allogeneic hematopoietic cell transplant (alloHCT) has been recommended for familial HLH, but its role in malignancy-associated HLH is unclear.[20] Our approach for the use of alloHCT in HLH is consistent with established expert guidelines.[20,21] In the setting on malignancy-associated HLH, we reserve alloHCT for relapsed or refractory cases, so alloHCT was not considered for the patients reported. Genetic testing for familial HLH-associated mutations was not performed for either patient given the secondary nature of their presentations and prompt resolution of HLH with treatment; however, HLH-associated mutations have been identified in patients with secondary HLH and may be helpful in decisions regarding the use of alloHCT.[20,21]

While outcomes for lymphoma-associated HLH have historically been poor, our results illustrate that R-CEPP is not only safe, but is an effective option for cHL-associated HLH, even in the setting of severe liver and/or kidney dysfunction. Both of our patients tolerated R-CEPP therapy well, and their outcomes were very encouraging. Furthermore, R-CEPP facilitated the definitive treatment for the underlying cHL, and should be considered for the initial treatment of cHL-associated HLH.

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Figure 1.

Bone marrow histology and immunohistochemistry. (A) Trephine sections showed classic Reed-Sternberg cells, with bilobed nuclei and inclusion-like, eosinophilic nucleoli (see arrow), characteristic of classical Hodgkin lymphoma. (B) Concentrate smears showed foamy macrophages with engorged erythrocyte precursors (arrow), as seen in hemophagocytic lymphohistiocytosis. (C) Trephine sections contained a 15% plasma cell population, characteristic of plasma cell myeloma. Plasma cells are best recognized by their eosinophilic cytoplasm and eccentric, clockface nuclei. (D) Staining the clonal plasma cell population for kappa (left) and lambda (right) immunohistochemistry showed a kappa-monotypic plasma cell population.