The novel use of emapalumab and ruxolitinib in acquired malignancy-associated hemophagocytic lymphohistiocytosis in pediatric patients

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal syndrome of immune dysregulation that is classified into primary and secondary forms. The standard of care is established with dexamethasone and etoposide, but there are currently no guidelines for refractory HLH or cases triggered by infection or malignancy. [1] We describe here a series of pediatric patients with malignancy-associated HLH (m-HLH) to discuss the complexities in the initial diagnostic considerations, the balance of therapeutic regimens and their toxicities, and the novel use of emapalumab and ruxolitinib in patients with refractory disease.

Title Page

Title: A case series: The Novel Use of Emapalumab and Ruxolitinib in Acquired Malignancy-associated Hemophagocytic Lymphohistiocytosis in Pediatric Patients.

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Abbreviation key:

HLH	Hemophagocytic lymphohistiocytosis
M-HLH	Malignancy-associated hemophagocytic lymphohistiocytosis
NK	Natural killer
B-ALL	B-cell acute lymphoblastic leukemia
COG	Children's Oncology Group
EBV	Epstein-Barr virus
sIL-2	Soluble interleukin-2
CXCL9	Chemokine (CXC motif) ligand 9
IFNγ	Interferon gamma
JAK	Janus kinase
IL-6	Interleukin 6

Abstract:

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal syndrome of immune dysregulation that is classified into primary and secondary forms. The standard of care is established with dexamethasone and etoposide, but there are currently no guidelines for refractory HLH or cases triggered by infection or malignancy. [1] We describe here a series of pediatric patients with malignancy-associated HLH (m-HLH) to discuss the complexities in the initial diagnostic considerations, the balance of therapeutic regimens and their toxicities, and the novel use of emapalumab and ruxolitinib in patients with refractory disease.

Main Text:

Introduction:

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of immune dysregulation leading to a hyperinflammatory state. HLH is categorized into primary and secondary forms. Primary, or familial HLH, is associated with known genetic mutations related to T and NK cell defects. Secondary HLH is an acquired form most often triggered by infection or malignancy in the pediatric population.

In the context of m-HLH in pediatric patients, the initial presentation presents a diagnostic conundrum. The HLH-2004 diagnostic criteria include clinical features of fever, splenomegaly, and cytopenia that overlap with infections and common malignancies of leukemia and lymphoma. [1] There are also similarities in treatment guidelines with the use of dexamethasone and etoposide. Patients are often critically ill upon presentation, which may prevent opportunities to carry out thorough diagnostic processes prior to treatment. This may lead to delays in diagnosis and treatment of an underlying malignancy. It also complicates the treatment of the malignancy with sub-optimal use of dexamethasone and etoposide that may allow for selection of chemotherapy-resistant cells. The histiocyte society recommends consideration of evaluation for malignancy for any patient suspected with HLH, but there are currently no established guidelines in pediatric patients to address the initial diagnostic workup, the primary treatment focus (HLH or malignancy), and the considerations for alterations of treatment regimens with respect to the toxicities of chemotherapeutic agents. [2]

We now discuss 3 patients with varying presentations of m-HLH with respect to severity, response, treatment considerations, and overall outcomes to demonstrate the spectrum of this hyperinflammatory syndrome.

Case Presentations:

Patient 1: A.T.

A 2-year-old African-American male presented with fevers and severe sepsis secondary to Streptococcus pyogenes bacteremia. Initial studies showed pancytopenia and hyperferritinemia which raised concerns for HLH and the patient was started on a 5-day course of dexamethasone. Evaluation for malignancy was attempted, but the patient became hemodynamically unstable with positioning during bone marrow biopsy and an inadequate sample was obtained with inconclusive results. Peripheral flow cytometry did not show presence of immature blasts. He met criteria for HLH and was treated with dexamethasone and etoposide per HLH-2004 and responded well without complications. However, 7 months after initial presentation, he presented with pancytopenia and was diagnosed with B-ALL. He was treated per COG-AALL1731 with persistent disease throughout induction and consolidation, which required the addition of blinatumomab. [3] His case raised the concern for an incomplete diagnostic approach during his initial HLH diagnosis that resulted in a false negative result that delayed the diagnosis of an underlying malignancy and partial treatment with dexamethasone.

Patient 2: A.M.

A 16-year-old female with persistent EBV-driven NK/T-cell lymphoma of the nasopharynx presented in septic shock with pancytopenia and disseminated intravascular coagulation. Initial diagnostic considerations included progressive lymphoma, bacteremia, and EBV viremia. HLH was a consideration,

but she did not meet criteria until hospital day 7. Treatment with dexamethasone, etoposide, and rituximab with her persistent EBV infection showed minimal effect. On day 17, a bone marrow biopsy showed evidence of NK/T-cell lymphoma and gemcitabine and oxaliplatin were started, but she developed acute decompensation with hemodynamic instability and multi-organ system failure likely due to fulminant EBV viremia. Her systemic inflammation worsened as evidenced by a rise in her ferritin, sIL-2 receptor, and CXCL9, a biomarker of IFNγ. [4] We held treatment for her lymphoma to reduce toxicities and better manage her HLH. With continued clinical deterioration, compassionate use of emapalumab, an IFNγ inhibitor indicated in primary HLH, led to dampening of her systemic inflammatory processes with resolution of fevers, decreased inflammatory markers, and signs of recovery of her hepatobiliary, renal, and gastrointestinal systems. [5] Unfortunately, despite demonstrating response to emapalumab, our patient succumbed to an intraparenchymal hemorrhage after developing fulminant candidiasis while on treatment dosing of micafungin.

Patient 3: J.P.

A 17-year-old Caucasian male presented with pancytopenia and proctitis and was diagnosed with T-ALL and treated per COG-AALL1231. [6] His course was complicated by bacteremia, fungemia, severe myelosuppression, and persistent fevers. He ultimately met HLH criteria and was treated per HLH-2004. Due to his myelosuppression, adjustments were made to both his chemotherapy and his HLH treatment. Reduced doses of dexamethasone were used, and etoposide was not introduced initially. Trials of IVIG and hydrocortisone showed minimal response. We then trialed ruxolitinib, a JAK 1/2 inhibitor shown to improve the inflammatory status of patients with HLH. [7] Although laboratory markers did not indicate resolution of his HLH, while our patient was on ruxolitinib, he had an overall improved quality of life. He had more energy, improved wound healing, and significantly fewer admissions for flares for 3 months. The effects of ruxolitinib eventually waned and our patient showed signs of hyperinflammation. Abdominal imaging demonstrated diffuse hepatic fungal micro-abscesses confirmed with biopsy. He was previously treated with courses of voriconazole and micafungin, but doses were adjusted due to incompatibility with his chemotherapy and concurrent toxicities. Treatment with a course of high dose fluconazole and repeat imaging showed resolution of the hepatic nodules. For his HLH, we trialed a course of etoposide, which was not used before due to his myelosuppression, but HLH did not improve. With our patient's fungal infection controlled, we began a trial of emapalumab for 2 months and resulted in progressive improvement of his inflammation, which has allowed for progression of his treatment for his T-ALL. Currently, his HLH and T-ALL both remain in remission and he has begun maintenance therapy for his leukemia while remaining on low-dose

hydrocortisone and ruxolitinib.

Discussion:

These cases highlight the intricacies of the management of m-HLH in pediatric patients with the spectrum of disease severity and complex diagnostic evaluations one must consider at presentation. Careful consideration must be taken with suspicion of HLH to carry out a thorough workup that will prevent delays in diagnosis for possible underlying malignancy.

The treatment of m-HLH is a delicate balance due to the myriad toxicities that arise from HLH and malignancy protocols. Although they are the backbone of HLH treatment, dexamethasone and etoposide may be inappropriate for some of the most unstable patients. This also highlights the importance of recognizing a lack of response to standard treatment to explore the use of investigational therapeutics for refractory cases in a timely manner. There is much to explore and learn from the use of novel therapeutics as with our patients who received emapalumab for their refractory HLH. Although they both demonstrated response to the addition of emapalumab, one of our patients may have succumbed to fulminant candidiasis as result of emapalumab. We theorize that as emapalumab blocks IFNγ, subsequently blocking neutrophil activation and IL-6 modulation, it led to our patient being more susceptible to systemic candidiasis, resulting in fungal emboli that led to her intraparenchymal hemorrhage. [8]

Due to the toxicity of treatment options required for concurrent processes of malignancy, infection, and HLH, novel therapeutics such as emapalumab and ruxolitinib are required and should be evaluated in larger studies. Considerations for the diagnostic approach of m-HLH should account for significant correlations like those seen in lymphoma-associated HLH and the sIL-2 to ferritin ratio. [9] Furthermore, guidelines for the management of pediatric m-HLH are required with inclusion of adjustments to standard therapy based on toxicity, inciting factors, concurrent infections, and the incorporation of novel therapeutics to lead to improved outcomes.

Conflict of interest statement: We have no conflicts of interests to disclose.

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