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Limitations of HLH-2004 criteria in distinguishing malignancy-associated hemophagocytic lymphohistiocytosis

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is characterized by dysregulated immune activation. Primary HLH involves hereditary deficits in cytotoxic lymphocytes while secondary HLH is triggered by extrinsic factors. The HLH-2004 criteria are widely used for clinical diagnosis, yet their specificity for HLH or their ability to differentiate primary from secondary disease is unclear, potentially leading to inappropriate treatment. We describe several cases where fulfillment of HLH-2004 criteria obscured the diagnoses of underlying malignancies and delayed curative management. These issues are remedied without waiting for genetic testing results through an alternative diagnostic approach using flow cytometry–based immunologic assays and a thorough investigation for malignancy.

KEYWORDS

diagnostic approach, hemophagocytic lymphohistiocytosis, oncology

1 | INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndromic disorder of immune regulation. Primary HLH results from underlying genetic defects in lymphocyte (natural killer [NK] and T-cell) cytotoxicity and requires HLH-directed therapy and allogeneic hematopoietic stem cell transplantation for cure. Conversely, secondary HLH is triggered by extrinsic pathology such as infection, rheumatologic disease, and/or malignancy. In secondary HLH, treatment of the underlying trigger(s) generally resolves immune dyregulation. Despite varying etiologies, differentiating primary and secondary HLH can be difficult due to indistinguishable clinical presentations, associated with excessive inflammatory cytokines and activation of macrophages.

Malignancy-associated HLH is a well-known entity in adults, with 48% of published cases being triggered by neoplasms.[1] Neoplasms as triggers of HLH in children have been recognized recently, with studies showing a prevalence of 8% to 11%.[2,3] The true incidence of malignancy-associated HLH may even be higher than those estimates, as some patients with immune dysregulation fulfilling the HLH-2004 diagnostic criteria in the context of malignancy may not have been recognized or reported, especially in pediatrics. Malignancy-triggered HLH is associated with increased mortality, with one pediatric series describing a 6-month overall survival of 67% and median overall survival of 1.2 years, with the majority of deceased patients having active malignancy at the time of death.[2] Thus, timely recognition and appropriate treatment of the malignancy is critical, as a misdiagnosis of primary HLH could result in the initiation of suboptimal or even incorrect therapy.

The prevailing standard to diagnose HLH utilizes the revised diagnostic criteria of the Histiocyte Society for the clinical study HLH-2004. The criteria stipulate that at least 5 of 8 clinical and laboratory

Abbreviations: ALCL, anaplastic large cell lymphoma; AMKL, acute megakaryoblastic leukemia; CBC, complete blood count; CCHMC, Cincinnati Children's Hospital Medical Center; CMV, cytomegalovirus; DLBCL, diffuse large B-cell lymphoma; DS, Down syndrome; DX, malignancy diagnosis; EBV, Epstein–Barr virus; FERR, ferritin; FIB, fibrinogen; FDG, fludeoxyglucose; HLH, hemophagocytic lymphohistiocytosis; HPC, hemophagocytosis; N/A, not assessed; NK, natural killer; NKF, NK cell function; PET/CT, positron emission tomography/computed tomography; PRF, perforin; sIL2R, soluble IL-2 receptor; TCL, T-cell lymphoma; TG, triglycerides; VUCS, variant of uncertain clinical significance; XLP, X-linked lymphoproliferative disease

TABLE 1 Patient demographics and diagnostic information

ID	Age at dx[a]	Sex	HLH-2004 criteria met	Fever[b]	Spleno-megaly	LOW CBC[c]	↑ TG ± ↓ fib[d]	HPC[e]	↓ / - NKF	↑ Ferr[f]	↑ sIL2R[g]	CD107a	PRF	SAP/ XIAP	Gene panel result[h]	DX
1	8 d	M	5/8	–	+	+	–	+	N/A	3071	40,570	Nl	Nl	Nl	VUCS in *PRF1*	ALCL
2	4 mo	M	7/8	+	+	+	+	–	+	1335	6530	Nl	Nl	Nl	Nl	Non-DS AMKL
3	8 mo	F	7/8	+	+	+	+	+	–	>40,000	11,572	N/A	Nl	Nl	Nl	EBV^+ TCL
4	2 y	F	6/8	–	+	+	+	+	N/A	836	13,327	Nl	Nl	N/A	VUCS in *UNC13D*	EBV^+ TCL
5	9 y	F	7/8	+	+	+	+	–	+	52,865	69,402	N/A	N/A	N/A	Nl	EBV^+ TCL
6	17 y	F	5/8	+	+	+	–	–	N/A	537	103,512	N/A	N/A	N/A	N/A	ALCL
7	18 y	M	6/8	+	+	–	+	–	+	6273	19,451	N/A	Nl	Nl	Nl	EBV^+ plasma-blastic lymphoma
8	21 y	F	8/8	+	+	+	+	+	+	>7500	10,225	Nl	Low	Nl	p.A91V + p.G149S in *PRF1*	Peripheral TCL
9	30 y	F	6/8	+	+	+	+	+	N/A	24,107	1489	N/A	N/A	N/A	N/A	DLBCL

Shaded column headings represent the HLH-2004 criteria.

[a] Age at the time of diagnosis of malignancy.

[b] Temperature >38.5°C for >7 days.

[c] At least two of three cytopenias present (hemoglobin <9 g/dl or in infants <4 weeks <10 g/dl, platelets $<100 \times 10^3/\mu$l, neutrophils $<1 \times 10^3/\mu$l).

[d] Defined as fasting triglycerides > 265 mg/dl and/or fibrinogen < 150 mg/dl.

[e] Hemophagocytosis noted in marrow, spleen and/or lymph nodes.

[f] Ferritin ≥ 500 ng/ml.

[g] Soluble IL2 receptor ≥ 2400 ng/ml.

[h] HLH gene panel run at CCHMC includes *AP3B1*, *BLOC156*, *ITK*, *LYST*, *MAGT1*, *PRF1*, *RAB27A*, *SH2D1A*, *SLC7A7*, *STX11*, *STXBP2*, *TNFRSF7*, *UNC13D*, and *XIAP*.

findings be present to diagnose HLH (Table 1). These guidelines were used as a research construct over a decade ago, before improved genetic and immunologic testing existed. Even with a high index of suspicion for HLH, strict use of the HLH-2004 criteria for diagnosis has pitfalls. Importantly, these criteria do not distinguish primary from secondary disease. Rather, they categorize a common phenotype characterized by toxic immune activation secondary to a range of disease processes, many of which have different treatments. Due to disease severity, treatment decisions are frequently made before genetic testing is complete. However, initiating primary HLH-directed therapy without careful consideration of potential underlying triggers can delay critical opportunities for appropriate diagnosis and curative treatment of the main pathology. We present here a series of nine pediatric and young adult patients in whom an initial diagnosis of HLH delayed the discovery of underlying malignancy and frequently delayed truly curative therapy.

2 | CASE DESCRIPTIONS

Table 1 provides demographic and diagnostic information for each patient. Ages ranged from 8 days to 30 years old. Each patient met the current requirements for the diagnosis of HLH, with ≥5 of the items specified in the HLH-2004 diagnostic criteria, with one patient having all 8. The two youngest patients had leukocytosis at presentation, while the others had normal or decreased white blood cell counts. Of the six patients for whom flow cytometry–based immunologic assays were performed, 5 (83%) had normal results. One patient (patient 8) had decreased perforin expression; she was found to be compound heterozygous for a known polymorphism and a mutation (p.A91V and p.G149S, respectively) in *PRF1* (perforin gene). Two other patients had a single variant of uncertain clinical significance (VUCS) found on sequencing a comprehensive panel of known HLH-associated genes (*PRF1* in patient 1 and *UNC13D* in patient 4). All others tested negative for known HLH-associated genetic mutations. Eighty-nine percent of patients tested positive for an infection at the time HLH was diagnosed (four with Epstein–Barr virus (EBV), one with EBV and concurrent influenza B, one with cytomegalovirus, one with methicillin-sensitive *Staphylococcus aureus* bacteremia, and one with pneumonia of unclear etiology).

Eight patients received HLH-directed therapy prior to malignancy diagnosis. Seven of these patients (patients 2–6, 8, and 9) were transferred to Cincinnati Children's Hospital Medical Center (CCHMC) after receiving dexamethasone and etoposide to treat HLH. Patient 7 was initially diagnosed with HLH at CCHMC and was treated with dexamethasone, but malignancy was detected shortly afterward and the patient was then switched to cancer-directed therapy. Of the 8 patients, only 2 (patients 2 and 8, 25%) had bone marrow evaluations performed beforehand. Of these, only 1 (patient 8) had adequate sampling (Figure 1A). None had neck-to-pelvis or whole body imaging prior to receiving HLH-directed therapy. Two of these patients (patients 8 and 9) had lymphadenopathy detected at diagnosis and underwent tissue sampling, though neither had positron emission

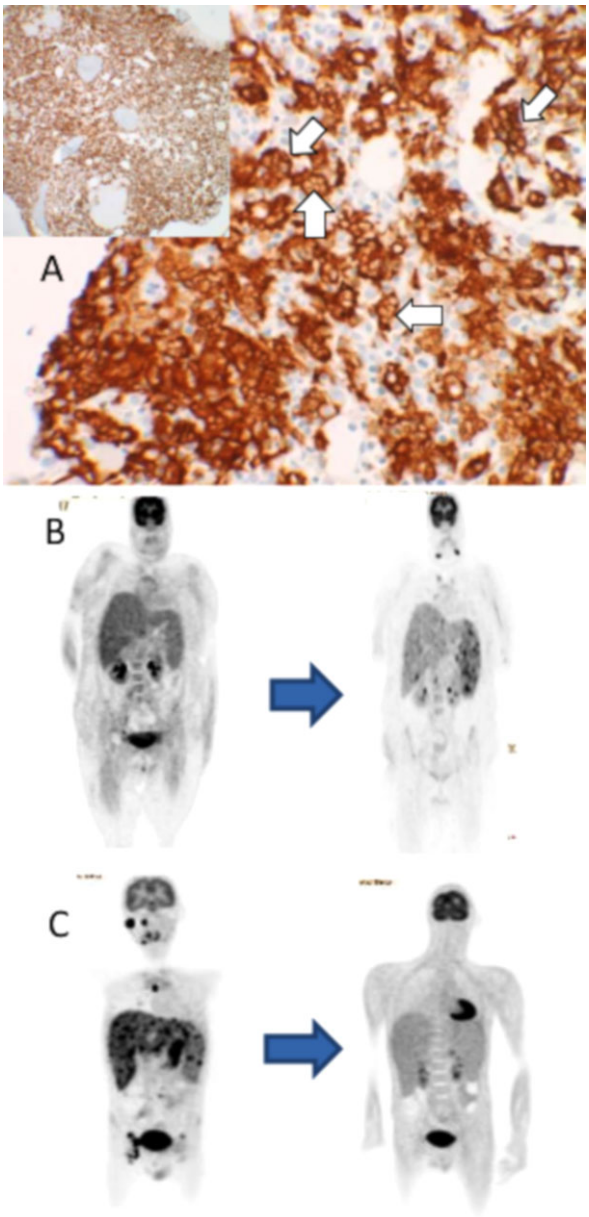

FIGURE 1 Imaging and pathology findings. (A), Bone marrow biopsy for patient 8, demonstrating histiocytic hyperplasia with hemophagocytosis. The arrows indicate histiocytes containing phagocytosed nucleated hematopoietic cells or red blood cells. CD163 immunohistochemistry demonstrates a pronounced, diffuse increase in bone marrow histiocytes (inset; original magnification ×100). On higher magnification (original magnification ×400), $CD163^{+}$ histiocytes are evident, many of which contain abundant cytoplasm. Images were captured by a Nikon Eclipse 80i microscope (objective lenses: Nikon Plan Fluor 10×/0.30, Nikon Plan Apo 20×/0.75, and Nikon Plan Apo 40×/0.95) using a Spot Insight Model 14.2 Color Mosaic camera with Spot Version 5.2 acquisition software. (B), PET/CT for patient 8. Image on the left was obtained while on high-dose steroids, and there were no findings concerning for lymphoma. Image on the right after wean to physiologic steroids, demonstrating multiple new FDG-avid lesions involving the liver, spleen, bone, and lymph nodes. (C), PET/CT for patient 7. Image on the left at diagnosis with multiple sites of abnormal FDG uptake (liver, spleen, small intestine, bone, lymph nodes). Image on the right after starting lymphoma-directed therapy, showing marked disease improvement

tomography/computed tomography (PET/CT) performed. Patient 8 had a fine-needle aspirate of a parotid lymph node and patient 9 had an excisional biopsy of an inguinal lymph node. In both cases, the results were nondiagnostic.

While undergoing treatment for HLH, many of the patients underwent imaging and/or bone marrow evaluations due to concerns for refractory HLH; these evaluations did not yield a diagnosis. The underlying malignancies were generally not discovered until HLH-directed therapy was discontinued for several days or weeks (Figure 1B), with the diagnoses being made by repeat bone marrow aspirate/biopsy (patients 2, 5, and 6), liver biopsy (patients 3 and 7), or excisional biopsy of an fludeoxyglucose (FDG)-avid node detected on PET/CT (patients 4, 8, and 9). Based on experience, an upfront lymph node biopsy was actively pursued for patient 1, even though the suspicion of primary HLH was high in an infant whose condition fulfilled the HLH-2004 diagnostic criteria.

All except one (89%) of the patients in our cohort were found to have a lymphoma, with T-cell lymphoma (including ALCL) being the most common category (67%) and EBV-positive T-cell lymphoma of childhood the most common specific type (33%). Unfortunately, by the time a diagnosis of malignancy was obtained, the majority (78%) were unable to receive full doses of first-line chemotherapy due to infections and/or organ dysfunction. All of these patients ultimately died from multiorgan failure with active malignancy present. Both patients who received full-dose chemotherapy (patients 1 and 7) are still alive with no evidence of disease (Figure 1C).

3 | DISCUSSION

An increased awareness over the last several years of the entity of HLH, and of the HLH-2004 diagnostic criteria, has seemingly led to more frequent diagnoses.[4] However, this awareness has often been accompanied by a narrow interpretation of the diagnostic criteria, raising the potential for a misinterpretation of secondary HLH as primary disease. Malignancy, infection, autoimmune disease, and primary HLH should all be considered probable in cases where the criteria are fulfilled. Primary HLH is more likely with positive family history or in children when all other diagnoses have been reliably excluded. In general, for secondary HLH, the likelihood of malignancy as an underlying etiology increases with age.[5] However, as our cases demonstrate, it should still be considered even in infants and young children. Although hematologic malignancies are responsible for the majority of malignancy-associated HLH, it has also been seen with solid tumors.[4]

The HLH-2004 diagnostic criteria were developed based on empiric observations in primary HLH using the available technology and disease knowledge at the time.[6] The specificity of these criteria in differentiating primary versus secondary HLH has not been thoroughly evaluated. The criteria largely consist of nonspecific markers of inflammation. These include the findings that are often mistakenly considered more specific for HLH, such as elevated soluble IL2 receptor (sIL2R) and hemophagocytosis.[7–9] Rubin et al also recently demonstrated that the NK cell cytolytic assay is neither efficient nor reliably diagnostic for primary HLH, with a sensitivity of 60% and a specificity of 72%.[10] Although the HLH-2004 diagnostic criteria do specify that there should be no evidence of malignancy and do include tissue hemophagocytosis as one of the laboratory findings, specific investigations to rule out an underlying cancer, such as imaging and tissue biopsy, are not explicitly mandated and the HLH-2004 criteria can be fulfilled without these studies. As evident from the presented patients, fulfillment of the HLH-2004 criteria is not sufficient to exclude malignancy.

It is notable that nearly all patients in our cohort tested positive for an infection at the time of diagnosis of HLH. In several cases, this led to a diagnosis of infection-associated HLH and initiation of HLH-directed therapy, without imaging studies or tissue evaluation to rule out malignancy. It is important to proceed with a thorough search for a malignancy, even when infectious testing is positive, especially because an infection like EBV could be the driver of lymphoma, as was seen in 4 patients with EBV^+ T-cell lymphoma and another with EBV^+ plasmablastic lymphoma.

Historically, one factor that may have limited diagnostic evaluations for malignancy had been the issue of time. It has been a generally accepted mantra that discernment of secondary from primary HLH is often not possible immediately and should not delay the initiation of therapy, as these patients are often acutely ill with organ dysfunction at presentation.[11] This thought process fails to account for two major realities of diagnosing HLH. First, as illustrated here, neglecting to rule out malignancy before starting HLH-directed therapy could confound subsequent investigations, especially imaging but potentially even tissue evaluations. By missing the diagnosis of an underlying malignancy until a patient is reevaluated for "refractory HLH," the appropriate curative treatment is delayed. This risks significant morbidity and often mortality, as was seen in our cases, and even promotes the possible selection of resistant clones and progression of the neoplasm while being given suboptimal anticancer therapy. These delays increase the risk of opportunistic infections and multiorgan dysfunction, which ultimately may limit the use of definitive treatments. As demonstrated here, only patients 1 and 7 ultimately received full-dose chemotherapy and they were the only ones to survive and achieve long-term remission.

The second reason to not pursue the reactionary approach of immediate HLH therapy once at least 5 criteria are present is the availability of tools to attain crucial evidence supporting primary versus secondary disease in a matter of days, not weeks. Certainly, the definition of primary HLH is based on the finding of HLH-associated gene mutations affecting NK and T-cell cytotoxicity, most of which are recessive (autosomal or X-linked). Sequencing-based gene panels offer a reliable screen for mutations (Table 1, legend). However, these genetic tests take several weeks to result. Additionally, as demonstrated in the case of patient 8, mutations in an HLH-associated gene do not preclude malignancy. Furthermore, distinguishing mutations from polymorphisms can be challenging. Finding single allele or digenic mutations adds further confusion because they do not automatically imply defects in lymphocyte cytotoxicity. A presumption of primary HLH on the basis of genetic variants that are not clearly pathogenic can be erroneous. To avoid these genetic testing delays, we utilize flow

cytometry–based immunologic assays to aid in diagnosis of primary HLH and expedite decisions on whether to initiate HLH-directed therapy.[11] T- and NK cell cytotoxicity is mediated by release of preformed cytolytic granules ("degranulation"), allowing perforin to form pores in the target cells through which cytotoxic granzymes enter.[12] Therefore, cytotoxicity can be evaluated by flow-cytometric measurement of lymphocyte perforin expression, while degranulation can be assessed via flow-cytometric measurement of CD107a. Additionally, flow cytometry is available to detect the expression level of intracellular gene products, SAP, which is low/absent in X-linked lymphoproliferative disease (XLP)1, and XIAP, which is low/absent in XLP2. In males, both XLP1 and XLP2 are among the potential genetic etiologies of HLH. All these assays usually result within a few days, minimizing the aforementioned treatment delays. Importantly, the tests can still be performed after starting treatment, provided sufficient lymphocytes are still present in circulation. If all flow cytometry tests are negative, the diagnosis of primary HLH should be questioned. These assays also aid in the interpretation of previously undescribed genetic variants, as normal results markedly decrease the likelihood of a variant being pathologic.

The clinical context must also be considered when trying to determine the presence of primary HLH. Certain "red flag" findings, which are not addressed in the HLH-2004 diagnostic criteria, make primary HLH exceedingly unlikely. For example, leukocytosis or significant lymphadenopathy are not typical features of primary HLH and should prompt diagnostic reconsideration, even if all 8 diagnostic criteria are fulfilled. Additionally, in adults the sIL2R/ferritin ratio has been shown to be higher in lymphoma-associated HLH.[13] Our cases support having a high concern for malignancy-associated HLH (especially lymphoma) when the sIL2R is disproportionally high compared with the ferritin (patients 1, 4, 6, and 7). Yet we also recognize that while all of these findings are useful in raising suspicion for malignancy-triggered HLH when present, the absence of these findings does not rule out malignancy either.

If HLH is suspected in a patient, we recommend a comprehensive evaluation, incorporating the flow cytometry studies for HLH and diagnostic studies for underlying triggers of secondary HLH. A printable algorithm that we use can be found at this link https://www.cincinnatichildrens.org/-/media/cincinnati%20childrens/home/service/h/hlh/clinical/test/genetic-testing-algorithm.pdf?la=en. In the absence of leading clues (e.g., blasts on peripheral smear, mediastinal mass on chest X-ray) and if flow cytometry–based immunologic assays are negative or equivocal, diagnostic pursuits must include investigations such as bone marrow aspirate and biopsy, CT scans of neck/chest/abdomen/pelvis, blood PCR for viruses, and if any neurologic concerns are present, brain MRI and lumbar puncture with cell count and morphology analysis. Ideally, the diagnostic CTs could be combined with a PET scan, as several of our cases showed the enhanced diagnostic utility of using PET/CT to target a particularly FDG-avid lymph node or lesion to biopsy. We also emphasize the importance of biopsy quality, as negative bone marrow results with suboptimal sampling do not rule out leukemia, and negative fine-needle aspirate results cannot substitute for an excisional node biopsy to exclude lymphoma.[14] In rare situations, an underlying malignancy may not be diagnosed despite proper lab/imaging/tissue evaluation or because the patient is so critically ill that HLH-directed therapy is needed immediately for survival. In cases where there is concern for "refractory" or "recurrent" HLH despite HLH-directed therapy, the full malignancy diagnostic workup should be completed or repeated. It is important to note that discontinuation, or at least significant weaning, of HLH-directed therapy is often required in order to obtain accurate diagnostic results. In these situations, we recommend discussions with centers that have expertise in treating patients with HLH.

For all patients in this cohort, the diagnosis of malignancy prompted a shift to cancer-directed therapy, but based on experience with other patients referred to our institution this is not always the case. In fact, the "HLH" label, despite recognition of the underlying malignancy, often leads to uncertainty about whether to treat the HLH or the malignancy, prolonging the delay of curative therapy. Similar confusion might plague the other forms of secondary HLH as well. HLH-directed therapy is sometimes needed prior to or in addition to cancer-directed therapy for symptom control, but nevertheless therapy targeted toward the malignancy should be initiated as soon as safely possible.

Our cases highlight the importance of understanding the limitations of the HLH-2004 criteria, especially in distinguishing malignancy-associated HLH. Given the improved diagnostic techniques, the nonspecific nature of the HLH-2004 criteria, and the high risk of delaying appropriate therapy for secondary HLH, we argue for the need to revise the diagnostic approach to HLH in order to limit morbidity and mortality in this challenging clinical situation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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