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ORIGINAL ARTICLE

Diagnostic Challenges in Pediatric Hemophagocytic Lymphohistiocytosis

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of severe immune dysregulation that encompasses a broad range of underlying genetic diseases and infectious triggers. Monogenic conditions, autoimmune diseases, and infections can all drive the phenotype of HLH and associated immune hyperactivation with hypercytokinemia. A diagnosis of HLH usually requires a combination of clinical and laboratory findings; there is no single sensitive and specific diagnostic test, which often leads to "diagnostic dilemmas" and delays in treatment initiation. Ferritin levels, one of the most commonly used screening tests, were collected across a large tertiary care pediatric hospital to identify the positive predictive value for HLH. Herein, we present several cases that illustrate the clinical challenges of confirming an HLH diagnosis. Additionally, we report on the utility of establishing a formal multi-disciplinary group to aid the prompt diagnosis and treatment of patients presenting with HLH-like pathophysiologies.

Keywords Ferritin · hemophagocytic lymphohistiocytosis (HLH) · immune dysregulation [3–6]

Introduction

HLH was first recognized as a disease of severe immune dysregulation in 1952, when the central features of fever, hemophagocytosis, hepatosplenomegaly, and progressive cytopenias were described [1]. Decades later, these sentinel features still represent cornerstone clinical indications to pursue further HLH diagnostic evaluations. Although HLH was initially characterized as a genetic disorder, we now know that this disease can also occur sporadically, often in association with infections, malignancies, or rheumatologic and autoinflammatory disorders. The etiologies of HLH differ between adults and children, but both populations display a number of conditions that could result in HLH [2].

Familial HLH is defined as immune dysregulation that is driven by mutations in one of four genes (*PRF1*, *UNC13D*, *STX11*, and *STXBP2*) that encode proteins involved in vesicle formation and trafficking [3]. These four monogenic conditions

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have a high penetrance, and patients are often prone to disease recurrence ("flares") until they undergo immune system replacement with allogeneic hematopoietic stem cell transplant (HSCT). Several other primary immunodeficiencies also have a high rate of HLH, including Chediak-Higashi syndrome due to mutations in *LYST*, Griscelli syndrome due to mutations in *RAB27A*, and Hermansky-Pudlak syndrome type 2 due to mutations in *AP3B1*, which collectively comprise the pigmentary dilution conditions associated with HLH. Other primary immunodeficiencies also have significant association with HLH, and treatment approaches are usually directed against the specific underlying immune defect [4].

In contrast, in the absence of an identified genetic cause, secondary or acquired HLH can be triggered by severe infections, autoimmunity, or malignancy [5]. Such patients often represent a diagnostic conundrum, as infectious etiologies can also trigger the first manifestations of primary or familial HLH. Moreover, HLH occurring in the setting of non-monogenic rheumatologic or autoinflammatory disease is often termed macrophage activation syndrome (MAS) [6]. HLH-like processes can also occur in the setting of metabolic conditions such as lysinuric protein intolerance, Wolman syndrome, and Gaucher's disease; treatment in these cases relies upon correction of underlying metabolic imbalances. Finally, certain immunotherapies used for cancer treatment, including chimeric antigen receptor (CAR) T cells, can lead to cytokine release syndrome (CRS), which clinically and biologically is diagnosed as HLH when severe. As such, classification of primary versus secondary HLH can be complicated given the myriad of potential triggering stimuli, heterogeneity of underlying genetic causes, and the clinical overlap in the pathophysiologic presentations of these diseases.

While no single diagnostic test exists for HLH, a set of criteria was recommended by the Histiocyte Society for use in the HLH-2004 research protocol and was revised in 2007. These criteria include identification of an HLH-associated gene defect and/or the presence of at least five of the following eight criteria: (1) fever, (2) low or absent natural killer (NK) cell function, (3) cytopenias, (4) splenomegaly, (5) increased triglycerides or low fibrinogen, (6) high ferritin, (7) hemophagocytosis, and (8) elevated soluble CD25 (interleukin 2 receptor alpha (IL2Rα)). Among patients with validated HLH, each criterion has a frequency of 71–95% [7] but individually has a low specificity for HLH [8, 9]. To better understand the diversity of conditions associated with increased ferritin, a key indicator of HLH, we used data from a structured database we established as part of the multi-disciplinary Immune Dysregulation program that was founded at our institution in 2018. This team includes pediatric geneticists, hematologists, immunologists, neurologists, oncologists, pathologists, rheumatologists, and infectious diseases specialists. We observed low positive predictive value for hyperferritinemia in pediatric HLH, and we present several cases in which the underlying diagnosis represented a particular diagnostic challenge in order to emphasize the diversity of conditions with clinical overlap with HLH.

Methods

This report is a single-institution retrospective chart review of patients with markedly elevated ferritin levels admitted to the Children's Hospital of Philadelphia (CHOP) between January 1, 2019, and January 1, 2020. This study was determined to be exempt from human subjects research approval by the CHOP Institutional Review Board. This project began as a quality improvement initiative to prospectively and systematically screen all children and young adults that were seen during an inpatient or outpatient visit at CHOP who had a single or multiple elevated ferritin value. A daily EPIC query was used to generate a log of all patients with a ferritin of > 500 μg/L. This log was reviewed daily by members of the Immune Dysregulation Team to identify patients in whom multidisciplinary consultation could have led to more timely diagnoses of HLH or other disorders of immune regulation. Data were maintained in a secure encrypted REDCap® database. To study this population comprehensively and to ascertain the potential specificity of hyperferritinemia, patients were further analyzed and classified according to age, sex, ethnicity, and primary diagnosis or underlying trigger and were grouped into the following categories: HLH/MAS, allogeneic or autologous stem cell transplant, malignancy, toxicities related to immunotherapy (e.g., CRS from chimeric antigen receptor T cell therapy/bi-specific T cell engager antibody immunotherapy), iron overload from chronic transfusions, infection, liver failure, and other (including metabolic disorders such as methylmalonic acidemia, MDA5+ associated interstitial lung disease, and necrotizing enterocolitis).

Statistical analysis was performed using Prism 8 (Version 8.2.0, Graphpad Software, La Jolla, CA) using analysis of variance (ANOVA) testing for group comparisons. Significant results are denoted by p value < 0.05.

Results

We analyzed a total of 163 patients with ferritin > 500 μg/L and patients were separated into the following categories: HLH/MAS ($n = 8$), allogeneic or autologous stem cell transplant (HSCT) ($n = 4$), malignancy ($n = 16$; $n = 9$ hematologic malignancy, $n = 7$ solid tumor), toxicities related to immunotherapy ($n = 33$), iron overload from chronic transfusions ($n = 83$), infections ($n = 8$), liver failure ($n = 2$), and other ($n = 9$) (Fig. 1). HLH/MAS was diagnosed based on fulfilling the HLH criteria, use of clinical judgment, serum cytokine levels and other biomarkers, and/or identification of a commonly associated HLH predisposing gene.

Ferritin levels ranged from a low of 2010 to a high of 148,220 μg/L. Although only 8 of 163 patients met HLH diagnostic criteria, a total of 17 patients had ferritin levels > 10,000 μg/L (Table 1). This includes 3/8 patients with HLH, 1/4 patients post-HSCT, 1/13 patients with cancer, 6/33 patients treated with chimeric antigen receptor T cell/bi-specific T cell engager therapy, 3/83 patients with iron overload, 2/8 patients with infections, 0/2 patients with liver failure, and 1/9 patients in the "other" category. Ferritin of > 10,000 μg/L had a positive predictive value of 18% at our institution, demonstrating that marked hyperferritinemia was not a specific biomarker for HLH in a tertiary care pediatric center. Although severe hyperferritinemia was seen among patients with the various diagnoses, those with HLH/MAS had statistically significantly higher mean ferritin levels ($p = 0.005$ by one-way analysis of variance [ANOVA]) when compared to other categories (Fig. 2).

Table 1 Maximum, average, and median ferritin levels observed across disease categories

	μg/L (range)
HLH/MAS (n=8)	
Max	195,590 (2588–195,590)
Average	33,276
Median	6598
Stem cell transplant (n=4)	
Max	23,883 (2113–23,883)
Average	7614
Median	2230
Malignancy (n=16)	
Max	74,660 (2397–74,660)
Average	8300
Median	3020
Immunotherapy toxicities (n=33)	
Max	64,231 (2030–64,231)
Average	7964
Median	3703
Iron overload (n=83)	
Max	19,203 (2130–19,203)
Average	3536
Median	2627
Infections (n=8)	
Max	148,220 (2215–148,220)
Average	22,152
Median	2631
Liver failure (n=2)	
Max	2944 (2042–2944)
Average	2493
Median	2493
Other (n=9)	
Max	41,620 (2101–41,620)
Average	7107
Median	2525

Illustrative Cases

Diagnosis of HLH requires identification of five of eight clinical criteria when a causal gene mutation is not identified. As these criteria may evolve sequentially or be incomplete, there is a true art to the early diagnosis of HLH. These cases herein represent significant diagnostic challenges and are described to provide context for ongoing evolution of the diagnosis and management of HLH beyond typical known causes. Table 2 presents the diagnostic characteristics of 17 patients without familial HLH who were evaluated by our multi-disciplinary Immune Dysregulation Team when HLH became a diagnostic consideration. Not all patients fulfilled the complete classical diagnostic criteria for HLH, and only a few children received standard HLH therapy. We classify patients by their ultimate diagnoses into four categories: (1) metabolic diseases, (2) rheumatologic diseases, (3) primary immunodeficiencies, and (4) infectious etiologies where the pathogen was considered to be the driving force leading to hyperinflammation. Referrals to our Immune Dysregulation Team were made based on clinical features suggestive of HLH, while in others, laboratory features suggested the diagnosis. The ultimate identification of an etiology occurred after multi-disciplinary dialog, targeted investigations, and revisiting the evolution of patients' clinical course over time.

Discussion

The Histiocyte Society established the first set of diagnostic guidelines for HLH in 1991 [10] and the first prospective international treatment protocol (HLH-94) in 1994 [11]. Revisions to both diagnostic criteria and treatment strategies were subsequently made with inclusion of three additional diagnostic criteria in the HLH-2004 protocol, including low or absent NK cell activity, hyperferritinemia, and high levels of soluble CD25 [12]. Given the relative non-specificity of the individual criteria, a diagnosis of HLH requires that at least five of the eight criteria be fulfilled unless a molecular mutation/diagnosis consistent with HLH has been identified. To highlight the complexity of HLH diagnosis in children, we analyzed a dataset from our Immune Dysregulation study.

Hyperferritinemia can occur in various disease processes including sepsis, infection, liver failure, malignancy, and HLH [13]. Previous studies have shown that a ferritin level of > 500 μg/L is > 90% sensitive for HLH, but specificity is only robust at levels of > 2000 to 10,000 μg/L [14]. Results from our institution confirmed this conceptual conclusion and supports the non-specificity of hyperferritinemia as a single biomarker in diagnosing HLH. As a ubiquitous iron-binding protein that regulates iron storage and homeostasis, the ferritin heavy chain gene is regulated by oxidative stress as well as pro-inflammatory signaling through the NF-κB pathway [13,

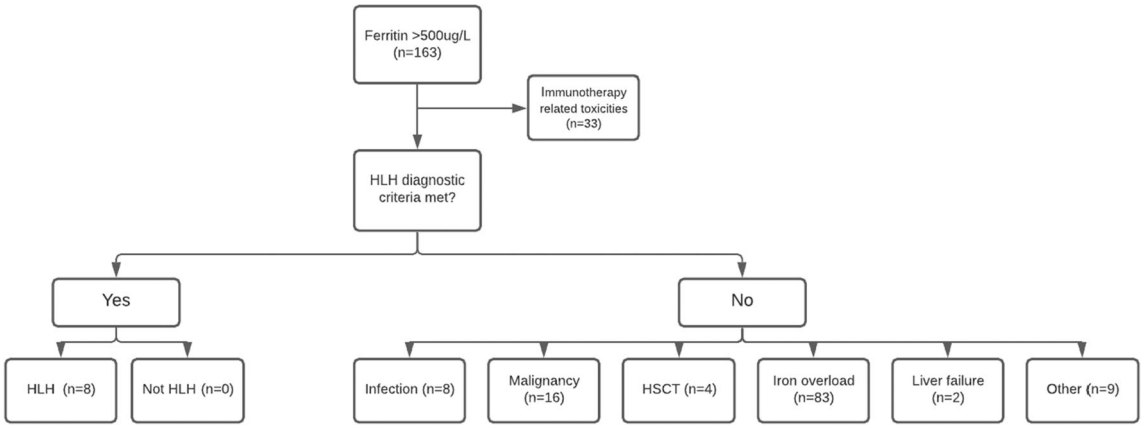

Fig. 1 Flow chart representation of various diagnoses associated with hyperferritinemia, highlighting its non-specificity as a single biomarker in diagnosing HLH

15]. Our data emphasize the range of conditions in which hyperferritinemia occurs and tabulate the sensitivity and specificity of ferritin > 10,000 μg/L, further highlighting the many opportunities for diagnostic confusion. Our data set predates the COVID-19 pandemic, although current utilization of the hyperinflammation index to identify patients at high risk of severe diseases also relies on some of the same criteria used for diagnosing HLH [16, 17]. While it is widely recognized that individual criteria are insensitive and non-specific for HLH, the actual application of these composite criteria in the setting of an acutely ill child where HLH is on the differential diagnosis can be quite complex. We describe illustrative patient cases with non-straightforward diagnoses to highlight the diagnostic challenge of simultaneously entertaining multiple etiologic possibilities of disease.

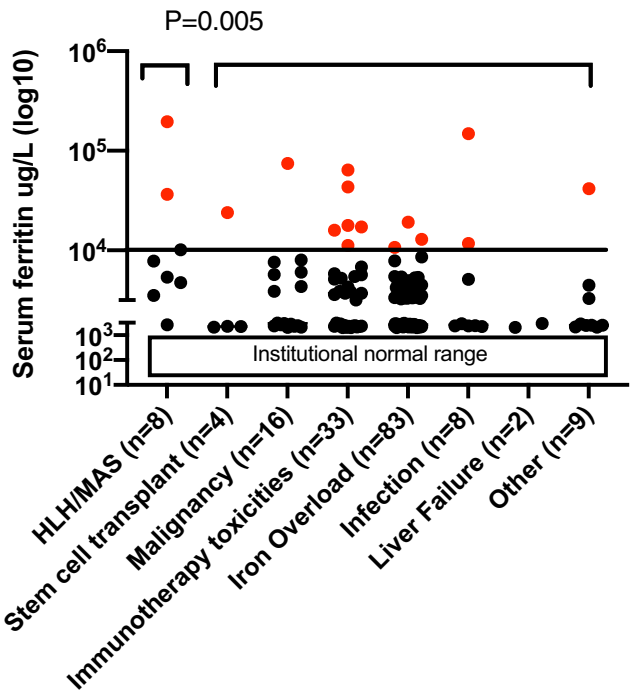

Fig. 2 Peak ferritin concentrations across disease categories. Severe hyperferritinemia were seen in various diagnoses, but patients with HLH/MAS had statistically significantly higher mean ferritin levels when compared to other categories

Secondary HLH in setting of infections, malignancies, and underlying immunodeficiency without a known monogenic cause of HLH are a particular concern, as the required treatments can be quite different. Interactions of pathogens with undefined aspects of host responses are thought to underlie HLH in these settings. Advances in our understanding immune function, along with increasingly-available scientific tools such as WES and WGS, will surely continue to expand our knowledge of HLH beyond the common gene mutations classically associated with primary HLH [2, 18] and identification of polymorphisms in known genes [19]. Our patient cases demonstrate the varied underlying conditions where HLH-like features can be seen and in which underlying immune compromise and/or specific infectious pathogens contributed to immune dysregulation. While allogeneic HSCT was performed for several patients to correct their underlying immune dysfunction, other children who did not undergo HSCT were treated with approaches intended to quell inflammation and allow re-establishment of immune homeostasis. In settings of acute infection, it can be challenging to distinguish whether the key driver of inflammation is an infection or whether host dysfunction is the central underlying pathologic process. In these challenging cases, our Immune Dysregulation Team, comprised of the specialties described above, initially is contacted through a rapid-response list-serve. The on-call member, a dedicated nurse practitioner, and the responding specialists will provide a response within 24 h for these critically ill children. The entire team reviews patients' charts in detail during a weekly multidisciplinary conference and weigh the benefits and limitations of different therapeutic approaches in these complex patients. As the patient's status evolves, the discussions continue. If

Table 2 HLH as a manifestation

Fulfilled HLH criteria?	**No**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	Yes	Yes	Yes	No
Fever >7d	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	2d of fever	Yes	2d fever	Yes	Yes	Yes	No
Cytopenias	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Splenomegaly	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Hepatomegaly	Yes	Yes	No	Infarcted
Triglycerides*	76	271	212	542	295	264	486	368	345	1280	289	474	ND	509	283	408	ND
Fibrinogen#	93	332	226	178	233	83	62	85	180	137	257	67	152	134	414	89	≤45
Ferritin*	2506	14,100	423	595	2835	1420	18,100	59,000	6050	1800	95,000	46,000	148,220	>40,000	9390	15,100	>40,000
Soluble CD25*	671	1743	ND	ND	5360	5055	44,200	13,530	1580	5808	22,700	87,600	6040	9330	1039	3130	1247
Low, Absent NK function	ND	Yes	NDadam	ND	Yes	Yes	ND	No	No	No	ND	ND	ND	ND	ND	ND	ND
Hemophagocytosis	ND	ND	None	Yes	ND	Yes	ND	Yes	Yes	No	ND	Yes	ND	ND	ND	Yes	ND
Age at presentation	2d	13y	10y	16y	10y	18y	14m	2m	2m	2y	2d	9y	8d	19y	15y	9y	Birth
Known pre-existing susceptibility	Pneumonia	Spinomuscular atrophy II- not a known risk factor	None	JIA	Pneumonia	Crohn colitis	CGD	None	WAS	22q11.2 deletion syndrome	None	None	None	Aplastic anemia s/p HSCT and engrafted	Osteosarcoma on chemotherapy	None	None
CXCL9	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	72pg/ml (<121 normal)	NS	285pg/ml (<121 normal)	NS	NS	NS	984 pg/ml (<121 normal)
Ultimate diagnosis	Argininosuccinate lyase deficiency	Lysinuric protein intolerance	sJIA	Parvovirus in JIA	MDAS+ JDM	EBV in Crohn colitis	*Burkholderia cepacia* in CGD	Rotavirus in CGD	*Mycobacterium gordonae* in severe WAS	EBV and RSV in 22q11.2 deletion syndrome	NLRC4	EBV HLH (WES negative)	Enteroviral hyperinflammation	Toxoplasmosis in immune compromised	*Candida tropicalis* in immune compromised	Ehrlichia	Unknown, WES and mito sequencing negative
Treatment	Arginine, ravicti, diet	Etoposide, dexamethasone	Methylprednisolone, anakinra	Methylprednisolone, anakinra	Methylprednisolone, cyclophosphamide, tofacitinib, rituximab		Methylprednisolone, anakinra	HSCT	HSCT	Cyclophosphamide, rituximab, dexamethasone, IT MTX	Tadekinig, prednisolone	Dexamethasone, rituximab, etoposide, then HSCT for refractory disease	Methylprednisolone	Steroids, tocilizumab, infliximab	Ambisome then fluconazole	Anakinra, etoposide, dexamethasone then doxycycline	Antibiotics
Outcome	Mild-mod delay, no recurrence	Ongoing neurologic issues only	Off medications without recurrence	No recurrence	Ongoing therapy with MMF, Prednisone, IVIG	Deceased	Deceased of HLH	Well post-HSCT	Deceased	No recurrence off therapy	No recurrence, ongoing tadekinig	Well post HSCT	No recurrence	Deceased	No recurrence off therapy	No recurrence off therapy	No recurrence

*Peak during illness

Nadir during illness

ND not done

needed, outpatient follow-up is available through our Immune Dysregulation clinic.

Treatment of patients with HLH continues to be challenging, as refinements of protocols since HLH-1994 have not improved clinical outcomes [5]. Conventional therapies to date have aimed at dampening immune activation through non-specific mechanisms and comprised of chemotherapy known to increase risk of secondary malignancy (i.e., etoposide) and high-dose dexamethasone associated with increased risk of infection, osteonecrosis, and hyperglycemia [12]. In recent years, direct targeting of disease-driving pathways and avoiding myelosuppressive effects of etoposide and global immunosuppression has become possible. One such therapy is emapalumab, a fully human anti-IFN-γ monoclonal antibody, which was approved by the US FDA in 2018 for treatment of patients with refractory HLH after a study demonstrated an overall response rate in 17 of 27 (63%) patients with recurrent or refractory primary HLH (NCT01818492) [20]. Other potential precision therapies used in patients with HLH include other biologic agents that block cytokines, including anakinra (anti-IL1) and tocilizumab (anti-IL6R) [21, 22]. Optimal therapy requires clear understanding of the etiologic process(es) driving the HLH, a non-trivial endeavor that our cases highlight. As additional small molecule inhibitors (e.g., JAK inhibitors such as ruxolitinib, tofacitnib, baricitinib, and itacitinib [23–25]) become a reality, the importance of molecular diagnostics and precision therapeutics become even more important.

Although discoveries of novel molecular pathways and use of targeted immune modulating therapies have led to significant progress in the treatment of this disease, much work remains to be done. Our case series of children with unusual clinical presentations evoking HLH highlights the remarkable biologic and immunologic heterogeneity of this condition. Development of true biomarkers and sensitive and specific diagnostic tests remain the aspiration. Until such time as real time diagnostics are available, the clinical criteria for diagnosis remain in use. This study highlights the many alternative explanations for a high ferritin and the diagnostic difficulties often seen in a tertiary care pediatric center.

Author Contribution SJS and KES were involved in analyzing data and writing the manuscript. RP acquired data, and HB, BTF, NR, MPL, MP, EJB, DTT, and KES designed this research study. SJS, SKT, HB, BTF, JA, RP, NR, MPL, MP, EJB, DTT, and KES all reviewed and edited this manuscript prior to submission. All authors had substantial contributions to this manuscript.

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Availability of Data and Material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Yes, we consent for publication.

Conflict of Interest SKT receives research funding from Incyte Corporation and Gilead Sciences for unrelated studies and serves on the scientific advisory board of Aleta Biotherapeutics. HB is an owner of CSL Behring stock and is a consultant for Kriya Therapeutics. MPL is an advisory board member for Octapharma and Shionogi, is a consultant for Amgen, Novartis, Shionogi, Dova, Principia, Argenx, Rigel, and Bayer, and has received research funding from Sysmex, Novartis,

Rigel, and Astra Zeneca. DTT serves on advisory boards for Amgen, La Roche, Janssen, and Sobi. BTF's institution receives funding from Merck and Pfizer for research studies, and he also serves on a Data Safety Monitoring Committee for Astellas. These studies are not related to this project. The remaining authors declare no relevant conflicts of interest.

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