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NEPHROLOGY - REVIEW

Hemophagocytic lymphohistiocytosis: an update for nephrologists

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Abstract Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome caused by defective lytic capability of cytotoxic T lymphocytes and NK cells, which results in proliferation of benign hemophagocytic histiocytes. A cytokine storm ensues, and a severe systemic inflammatory response syndrome, multiorgan dysfunction syndrome, and death frequently follow. It may occur as a primary (inherited) form, or be acquired secondary to malignancy, infection, rheumatologic disease, or immunosuppression. Cardinal manifestations include fever, cytopenias, hepatosplenomegaly, and dysfunction of liver, kidney, CNS, and/or lung. Additional laboratory findings include marked hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, abnormal LFTs, coagulopathy, and hyponatremia. Nephrologists need to be aware of this syndrome owing to the frequent occurrence of acute kidney injury in these severely ill patients. Glomerulopathy and nephrotic syndrome may develop. Kidney transplant recipients are at increased risk of HLH due to immunosuppression, and most such cases are triggered by infection with over 50 % mortality. Effective treatment of HLH usually requires chemoimmunotherapy to acutely suppress inflammation, specific treatment of underlying infection or malignancy, and in certain cases hematopoietic stem cell transplantation. The pathogenesis, clinical manifestations, diagnosis, and treatment of HLH are discussed.

Keywords Hemophagocytic lymphohistiocytosis · Macrophage activation syndrome · Hemophagocytic syndrome · Acute kidney injury · Kidney transplantation · Systemic inflammatory response syndrome

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by a hyperactive yet ineffective immune response to an antigenic challenge. HLH results from either an inherited (primary) or acquired (secondary HLH) inability of cytotoxic CD^{8+} T lymphocytes (CTLs) and natural killer cells (NKs) to lyse target cells [1–4]. These target cells include the initiators of the immune response, such as infected or malignant cells, and antigen-presenting cells upon resolution of the initial challenge. The consequent proliferation of CTLs results in a large production of interferon-γ (INF-γ) that causes a marked proliferation of benign histiocytes (macrophages). These macrophages and CTLs invade organs, such as liver, spleen, and lymph nodes, and release further inflammatory cytokines, including INF-γ, TNF-α, and interleukins (IL)-1, 6, and 18 [5]. The result is a so-called cytokine storm with severe systemic inflammatory response syndrome (SIRS), multiorgan dysfunction syndrome (MODS), and frequent death. The proliferating histiocytes engulf red cells, white cells, platelets, and their precursors and are called hemophagocytes (HPC), hence the alternative designation hemophagocytic syndrome.

The cardinal clinical manifestations of HLH include unremitting fever, hepatosplenomegaly, various cytopenias,

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and multiorgan dysfunction, including liver, CNS, lung, and kidney [1–4]. Characteristic laboratory findings in addition to the cytopenias include hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, abnormal LFTs, hyponatremia, elevated LDH, elevated soluble CD25 (sCD25), reduced or absent NK cell activity, and coagulopathy. Bone marrow aspiration typically, but not always, reveals HPCs, which may also be seen in the liver, spleen, or lymph nodes. Unfortunately, no pathognomonic finding or test is available to diagnose HLH, including the presence of HPCs, as these may be found in otherwise severely ill patients [6, 7].

Nephrologists need to be aware of HLH [8]. Acute kidney injury (AKI) can develop, especially in the critically ill [9], where it may be challenging to differentiate HLH from severe SIRS/MODS secondary to sepsis, trauma, or autoimmune/autoinflammatory disease. The distinction is critical, as immunomodulatory therapy may be required to dampen the hyperinflammatory state if HLH has developed, but may be harmful otherwise. In addition, various glomerulopathies are reported in HLH, often in the setting of nephrotic syndrome [10]. Thrombotic microangiopathy (TMA) can also occur [10]. Finally, HLH can develop post-kidney transplantation [11].

Pathophysiology: primary HLH

Primary or familial HLH (FHL) results from recessive mutations in genes involved in the function of the cytotoxic granules of CTLs and NKs. Normal degranulation requires several proteins for cytosolic vesicle transport, sorting, docking, priming, and finally fusion with the cell membrane [12]. Upon degranulation, perforin inserts into the target cell membrane, thereby allowing granzymes to enter and cause apoptosis. At least 5 types of FHL are described, termed FHL1-5. They are detailed in Table 1. FHL usually presents in the first months of life, often in response to a viral infection or immunization. However, some patients present later in adult life (see below).

Other inherited immune deficiency syndromes also can present with HLH, including oculocutaneous albinism syndromes (Chediak–Higashi syndrome, Griscelli syndrome type 2, and Hermansky–Pudlak syndrome type 2), which share defective cytotoxic degranulation similar to FHL3-5. The X-linked lymphoproliferative diseases (XLP), types 1 and 2, have normal degranulation but develop HLH in response to uncontrolled primary EBV infection [13]. Additional primary immunodeficiencies that may develop HLH include severe combined immunodeficiency (SCID), combined immunodeficiency, and chronic granulomatous disease [14]. Interestingly, HLH can develop in SCID patients with severe deficiencies of both CTLs and NKs. Nevertheless, macrophages can be activated with an associated cytokine storm [14].

Mice bearing analogous mutations to those found in human FHL and other primary immunodeficiencies have been developed [3, 15]. The best studied are perforin-deficient mice ($Prf^{-/-}$), mimicking FHL2. These mice diseases do not develop spontaneously but require an infectious trigger, typically either the lymphocytic choriomeningitis virus (LCMV) or murine cytomegalovirus (MCMV). With LCMV, the full HLH syndrome develops, and the main pathogenic cytokine is INF-γ secreted by CD^{8+} CTLs. A somewhat more benign syndrome develops with MCMV. Although CTLs and NKs produce INF-γ to activate macrophages in this model, TNF-α secreted by macrophages and dendritic cells (DCs) is the main culprit, and IL-10 secreted by NKs tends to dampen the hyperinflammation. Analogous to FHL3 and FHL4, mice deficient in Munc13-4 ($Unc13d^{jinx/jinx}$) and syntaxin 11 ($Stx11^{-/-}$), respectively, have been developed. Again, they are susceptible upon viral challenge to develop an HLH-like syndrome with variations in severity and cytokine mediators.

With FHL, the severity of the cytolytic defect of CTLs in patients with biallelic null mutations correlates with severity of disease, at least in terms of age of onset [15]. Perforin deficiency, the most severe defect, has the earliest age of onset (mean age 3 months). The age of onset increases with Griscelli syndrome type 2 (13 months), FHL4 (27 months), and Chediak–Higashi syndrome (38 months), although high variability exists within each group [15, 16]. Similar graded defects in cytotoxicity correlate with the severity of disease in the corresponding murine models: Perforin-deficient mice demonstrate the most severe HLH, followed by Rab27A deficiency (Griscelli syndrome type2), syntaxin 11 deficiency (FHL4), and Lyst deficiency (Chediak–Higashi syndrome). Of note, restoration of perforin expression to 10–20 % of normal with mixed chimerism in a mouse model ($Prf^{-/-}$) reestablished normal immune regulation [17]. This is analogous to patients with hypomorphic missense mutations (as opposed to null mutations) who have reduced rather than absent protein expression. Such patients present later in life, with milder disease or atypical features [18–21].

Pathophysiology: secondary HLH

sHLH develops at any age without a detectable genetic defect. Inciting events include infection, malignancy, autoimmune/autoinflammatory disease, metabolic disease, and immunosuppression associated with HIV or solid organ transplantation [22–25]. An appropriate inflammatory response becomes exaggerated to produce a clinical syndrome similar to FHL. Polymorphisms or hypomorphic

Table 1 Genetic defects associated with HLH

	Syndrome	Mutated gene	Mutated protein	Function	Comments
FHL	FHL1	Unknown	Unknown	Unknown	10 % or less of FHL
	FHL2	*PRF1*	Perforin	Pore formation	30–50 % of FHL
	FHL3	*UNC13D*	MUNC13-4	Priming of cytotoxic granules	Early onset; CNS frequent
	FHL4	*STX11*	Syntaxin11	Fusion of cytotoxic granules	Rare; almost all of Turkish descent
	FHL5	*STXBP2*	MUNC18-2	Fusion of cytotoxic granules	Hypogammaglobulinemia; colitis
Syndromes with oculocutaneous albinism	Chediak–Higashi syndrome	*LYST*	LYST	Granule sorting	Recurrent pyogenic infections; abnormal granule size
	Griscelli syndrome type 2	*RAB27A*	RAB27A	Granule docking	Late onset; CNS frequent
	Hermansky–Pudlak-type 2	*AP3B1*	B-chain of AP3 complex	Granule trafficking	Rare cause of HLH
PID syndromes with enhanced susceptibility to EBV	XLP type 1	*SH2D1A*	SH2 domain protein 1A	Normal immune function of T cells, NK cells, and NKT cells	Primary EBV infection; hypogammaglobulinemia; propensity for lymphoma
	XLP type 2	*XIAP*	X-linked inhibitor of apoptosis	Normal NKT cell maturation	Mild or partial HLH: colitis
	ITK deficiency	*ITK*	Il-2-inducible T cell kinase	Normal NKT cell maturation	EBV-associated lymphoproliferative disease
	CD27 Deficiency	*CD27*	CD27	Binds CD70, T cell co-stimulation	EBV-associated lymphoproliferative disease; Hodgkin's; uveitis
Other PID	SCID	*ILR2G*	Common gamma chain	Normal maturation of B, T, NK cells	Fatal infections shortly after birth
		RAG1	Recombination activating gene 1	Normal maturation of B and T cells	Omenn syndrome
		IL7RA	IL-7 receptor-α	Normal T cell maturation	Multiple sclerosis
	CID	*WASP*	Wiskott-Aldrich syndrome protein	Normal T cell function	Wiskott-Aldrich syndrome
		Various genes		Normal neutrophil function	Chronic granulomatous disease

CID combined immunodeficiency, *FHL* familial hemophagocytic lymphohistiocytosis, *PID* primary immunodeficiency, *SCID* severe combined immunodeficiency, *XLP* X-linked immunodeficiency syndrome

mutations in the same genes that cause FHL may underlie susceptibility to sHLH (see below). A predisposing condition and/or triggering event can be identified in the majority of sHLH cases. Multiple causes may coexist, such as malignancy or immunosuppression with an infectious trigger. Occasionally, no inciting event is found and these cases are considered idiopathic. Since primary HLH can be initiated by the same triggering agents as those causing sHLH, an apparent diagnosis of sHLH does not rule out an underlying genetic defect.

The hyperferritinemia and hemophagocytosis characteristic of HLH both contribute to its pathophysiology and, simultaneously, help to mitigate the hyperinflammation. Ferritin is an intracellular, iron-storage molecule composed of 24 subunits [26]. Ferritin is secreted by hepatocytes, Kupffer cells, and macrophages in an iron poor form. Secreted ferritin has pro-inflammatory effects by stimulating production of NF-κB in hepatic stellate cells. Alternatively, lymphocytes may be stimulated to produce the anti-inflammatory IL-10. In addition, ferritin inhibits CXC chemokine receptor 4, thereby reducing proliferation and migration.

Anemia in HLH develops rapidly, and hemophagocytosis per se has been ascribed a primary role. Zoller et al. [27] termed this "consumptive anemia of inflammation" and showed that interferon-γ signaling is required for both the anemia and hemophagocytosis by a process resembling apoptotic cell uptake. Hemophagocytosis preceded anemia and was considered the major proximate cause. In a different model, Behrens et al. [28] produced severe anemia without detectable hemophagocytosis. Subsequently, this group confirmed the prime importance of interferon-γ for development of severe anemia but not for hemophagocytosis, which was readily detectable in interferon null mice in the absence of anemia [29]. Hence, hemophagocytosis was neither necessary nor sufficient for developing severe anemia.

Recent evidence indicates that the driving force for MODS in HLH is the cytokine storm and not hemophagocytosis [30]. In fact, HPCs can release significant quantities of the anti-inflammatory IL-10, representing a mechanism to dampen the hyperinflammation [31]. In a mouse model, blocking either hemophagocytosis itself or the IL-10 released from HPCs enhanced virus-induced CTLs, liver damage, and mortality [31]. HPCs express markers of alternate activation [32] (M-2 macrophages), including the hemoglobin/haptoglobin scavenger receptor CD163 [32]. M-2 macrophages contribute to resolution of inflammation and tissue repair [33]. Both free and bound hemoglobin can be taken up by CD^{163+} macrophages and can activate heme oxygenase-1 (HO-1) [34]. Similarly, CD^{163+} HPCs have upregulated HO-1 in response to free heme liberated from phagocytosed erythrocytes [35]. The HO-1 catabolism of heme results in production of ferritin, bilirubin, and carbon monoxide, agents with potent anti-inflammatory effects [36]. Interestingly, postmortem bone marrow samples of patients dying from sepsis revealed abundant HPCs expressing HO-1, thereby indicating role for hemophagocytosis in hyperinflammatory states in general [35].

HLH in adults

Ramos-Casals et al. [22] reviewed MEDLINE and Embase databases supplemented with manual searches through 9/2011 for case series dealing with the clinical manifestations and treatment of HLH in adults and found 677 articles (2197 patients). Mortality was 41 % in a subset of 1109 patients. Infections were identified in 1108 (of the 2197), neoplasms in 1047, autoimmune disease in 276, transplantation in 95 (including 53 kidney), and other circumstances in 89. Only 81 were idiopathic. Nearly a third had multiple causes. The most common infections were viruses (762 of 1108), mainly EBV (330) and HIV (173). Other viruses included CMV (69), other herpes viruses (74), parvovirus, hepatitis viruses, and influenza. Bacteria were found in 206/1108, most commonly tuberculosis (78), but also staphylococcus and E coli. The most common parasite was leishmania and histoplasma the most common fungus. Of 1047 neoplasms, the majority were hematologic (981), including 369 with T cell or NK cell lymphoma, 333 with B cell lymphoma, 67 with leukemia, and 61 with Hodgkin's lymphoma. Solid tumors were rare (32). The most common autoimmune diseases were SLE (133/276) and adult-onset Still's disease (AOSD) (54).

Subsequently, 3 large series of HLH in adults were published. Riviere et al. identified 162 patients [23]. Hematologic malignancies were the most common triggers (92 patients). Infections were identified in 40, including 6 with concurrent malignancies. Autoimmune disease was found in 5. Parikh et al. [24] reported 62 adult patients. They also found the most common cause to be malignancy (32 patients). Infection was found in 21, autoimmune disease in 5, and 4 were idiopathic. Li et al. [25] reported 103 cases. Again, hematologic malignancies were most common (49 patients). Infections were found in 24, autoimmune diseases in 14, 24 with an unknown origin, and 8 with multiple causes.

When complicating rheumatic diseases, sHLH is termed macrophage activation syndrome (MAS). Most commonly, this occurs in systemic onset juvenile idiopathic arthritis (sJIA) [37], AOSD [38], or SLE (childhood [39] or adult onset [40]). HLH can also complicate Kawasaki's disease or a vasculitis. With autoimmune or autoinflammatory conditions, HLH is typically triggered by a flare of the disease [37–39]. Less commonly, viruses such as EBV or antirheumatic medications are implicated.

HLH develops in about 10 % of cases of sJIA. Another 30–40 % evidence occult HLH [41–43]. Such cases have laboratory abnormalities consistent with HLH, but lack clinical manifestations [43]. When HLH complicates sJIA, 20 % of cases appear simultaneously with onset of the sJIA without frank arthritis and may be confused with FHL. Defective cytotoxic function of NKs occurs with HLH complicating sJIA, although a similar defect may be detectable in the absence of HLH [44].

Genetic considerations in adult HLH

The separation of primary HLH from sHLH is not clear-cut and should not be based simply on age of presentation. sHLH can present in childhood [45], and adults with sHLH may have genetic defects similar to the inherited conditions in Table 1. Realization of this overlap is important, because with an inherited mutation HLH may recur, and should the patient survive the initial episode prolonged therapy and/or hematopoietic stem cell transplantation (HSCT) need be considered.

Zhang et al. [21] studied 175 adult HLH patients referred for genetic testing. Missense and splice-site mutations/polymorphisms in the genes for perforin, MUNC13-4, and MUNC18-2 were found in 25 (14 %), including 12 (48 %) with the A91V polymorphism in both heterozygous and homozygous states. The A91V polymorphism reduces expression of perforin [46] resulting in susceptibility to HLH and is present in 3–17 % of the general population (1–4 % homozygous) [46]. Two patients were double heterozygotes with the A91V mutation and another mutation in one of the genes involved in degranulation. In a follow-up study, Zhang et al. [47] found an additional 21 patients with digenic heterozygous mutations involving perforin (10 of which had A91V) and one of the degranulation genes. Seven had digenic heterozygous mutations in 2 degranulation genes. These mutations/polymorphisms were considered hypomorphic, with adult HLH following a viral or other trigger. Sieni et al. [48] described 11 adult-onset patients with genetic defects underlying HLH in an Italian registry. These included 6 patients with biallelic perforin mutations, of which 4 included heterozygous A91V polymorphisms. Two also carried biallelic mutations consistent with FHL3, one FHL5, and 2 with XLP1. Wang et al. [49] studied 195 Chinese adults with HLH and found 3 with biallelic perforin mutations, 1 hemizygous SAP mutation (XLP1), and 6 monoallelic mutations (3 involving perforin, 3 syntaxin 11). None had the A91V polymorphism.

FHL mutations may also underly sHLH in the pediatric age range. In cases of HLH complicating sJIA, pathogenic biallelic *MUNC13-4* mutations were found in 2 of 18 patients [50]. Another study found the A91V perforin polymorphism in 20 % of 15 sJIA patients with HLH compared to 10 % of 41 sJIA patients without HLH [51]. Similarly, whole-exome sequencing of 14 sJIA patients with HLH found 5 with protein-altering variants in FHL-related genes (*MUNC13-4*, *STXBP2,* and *LYST*) compared to 4 of 29 patients with sJIA without HLH [52]. In a study of 28 patients with HLH, 13 had 1 or more mutations in HLH-related genes, including 5 with *STXPB2* and 5 with *UNC13* mutations [53].

Clinical manifestations

The clinical manifestations of HLH result from tissue invasion by macrophages and CTLs, as well as the "cytokine storm" from the excessive release of inflammatory cytokines, especially IL-1, IL-6, IL-18, INF-γ, and TNF-α. A constellation of symptoms, signs, and laboratory abnormalities occurs that depends on the severity of the syndrome, the underlying predisposing conditions, and the presence of a triggering agent. Unremitting fever is nearly universal. Other constitutional symptoms include asthenia and weight loss. Splenomegaly, hepatomegaly, and adenopathy occur in a significant minority. Neurologic manifestations may develop in up to 70 % of sHLH cases [54–57] and may be obvious clinically or detectable only by imaging or CSF examination [56]. Clinical findings include altered mental status, seizures, hemiparesis, cranial nerve palsies, and meningitis. Permanent sequelae may result [54, 56, 57]. Coagulation abnormalities are common. Disseminated intravascular coagulation (DIC) may occur in 50 % HLH patients in the ICU, with over 20 % having severe bleeding [58]. Liver dysfunction is common and can progress to fulminant failure. Histologically, portal tract infiltration by CTLs and HPCs is present [59]. Cutaneous manifestations occur in up to 65 % of patients and include erythroderma, maculopapular rash, and morbilliform eruption [60]. HPCs may be found in skin biopsies [61]. A systemic inflammatory response syndrome (SIRS) with multiorgan dysfunction syndrome (MODS) may occur, including shock and acute lung or kidney injury. The clinical manifestations of HLH overlap with other causes of SIRS or MODS, such as bacterial sepsis or trauma, and such cases may be incorrectly labeled as "culture-negative sepsis [62]". Patients dying from sepsis may have a marked proliferation of CD^{163+} HPCs predominantly ingesting RBCs and their precursors in the absence of frank HLH [35].

The most notable laboratory abnormalities in HLH include cytopenias, hyperferritinemia, hypofibrinogenemia due to consumption and liver injury, hypertriglyceridemia secondary to cytokine inhibition of lipoprotein lipase, and elevated transaminases and LDH. CRP may be markedly

elevated, but the ESR is often normal or only minimally elevated because of hypofibrinogenemia. Elevated soluble CD25 and soluble CD163 reflect excessive CTL and macrophage activation, respectively. NK cells or their function is markedly reduced. Hyponatremia is common.

The most frequent renal manifestation is AKI. Aulagnon et al. [9] reported on 95 ICU patients with sHLH. Using current definitions, AKI occurred in 59 (62 %); 6-month survival was 37 % as compared to 56 % in those without AKI. Most (51 patients) reached stage 2 or 3 AKI, and dialysis was required in 59 %. AKI was attributed to acute tubular necrosis (49 %), hypoperfusion (46 %), tumor lysis (29 %), or glomerulopathy (17 %). Only 1 patient had a kidney biopsy. Nephrotic syndrome (NS) was present in 12, of whom 9 had AKI. Thirty-two percent of surviving patients had CKD at 6 months. The incidence of AKI was no different from that in a contemporaneous group of newly diagnosed, high-grade malignancy patients admitted to the same ICU (58 % of 202 patients). Direct interstitial infiltration by activated macrophages and T lymphocytes is reported to cause reversible AKI [63].

Glomerulopathy and NS complicating HLH result from primary podocyte pathology. Thaunat et al. [10] reported on 9 patients with NS and HLH that had kidney biopsies at 3 French hospitals and another 2 cases from the literature. AKI was present in 10/11, and 7/11 died. The underlying lesions included collapsing FSGS (5 patients, all of African descent), minimal change disease (4 Caucasian patients), and TMA (2 patients). A subsequent case report found minimal change disease in association with HLH [64].

HLH can complicate kidney transplantation. In 1979, Risdall et al. [65] described 19 patients with virus-associated HLH, and 13 were kidney transplant recipients. All cases were triggered by viruses, predominantly CMV. Karras et al. [66] studied 17 patients with HLH among 4230 renal transplants (prevalence of 0.4 %) collected from 8 Parisian transplant units. HLH developed from 10 days to 15 years after transplantation (median 52 days). All 17 were receiving corticosteroids, and 11 had received ATG within 3 months prior to developing HLH. Infections were detected in 14, most commonly herpes viruses (3 EBV, 3 CMV, 1 HHV 6, and 1 HHV8). Two patients had lymphoma, and 2 had no obvious trigger. Immunosuppression was reduced in all. Eight died, and 4 of the 9 survivors lost their allografts. Asci et al. [67] reported on 13 patients out of 403 renal transplant recipients (prevalence of 3.2 %) from a center in Turkey. HLH occurred from 2 weeks to 30 months post-transplantation (median 15 months). An infectious trigger was identified in 6 (tuberculosis in 4, CMV in 2, *E. coli* in 1). Hepatitis C was present in 8 of the 13. All patients had azathioprine discontinued and CNI reduced or discontinued. All 6 patients that received IVIg survived, as did 2 other patients responding to antimicrobial therapy.

Table 2 Infectious triggers in kidney transplantation

	Organism	Number of cases	References
Viruses	CMV	24	[65–67, 76, 84, 85, 136, 137]
	EBV	6	[65, 66, 84, 138]
	HHV 8	5	[66, 67, 83, 86]
	HHV 6	2	[66, 82]
	BKV	2	[72, 87]
	VZV	1	[65]
	Parvovirus B19	1	[90]
	Hepatitis C	1	[66]
	HSV 1	1	[65]
	Dengue	1	[70]
Bacteria	Tuberculosis	6	[66, 67, 79]
	Bartonella	3	[66, 71, 74]
Parasites	Toxoplasmosis	4	[66, 88, 137]
	Babesiosis	2	[78, 139]
	Leishmaniasis	1	[75]
Fungi	*Torulopsis*	1	[89]
	Pneumocystis	1	[66]
	Histoplasmosis	2	[68]

In a 2009 *Editorial Review*, Ponticelli and Alberighi identified 76 cases of HLH in kidney transplant recipients with an overall 53 % mortality [11]. The majority of cases were triggered by infections, most commonly viral, but also bacterial and protozoal infections. HLH also occurred in patients with malignancy. Subsequently, additional cases of HLH in kidney transplant recipients have been reported with a variety of triggers, typically infections [68–74], including histoplasmosis, dengue, *Bartonella,* CMV, and BK virus. To date, 84 kidney transplant patients have been reported to have HLH [65–90]. Infectious triggers were identified in 76 % (Table 2).

Diagnosis of HLH

No pathognomonic finding or test confirms HLH. The Histiocyte Society proposed criteria for diagnosing pediatric FHL (Table 3). According to the most recent update (HLH-2004) [91], 5 of the following 8 criteria must be satisfied: (1) fever; (2) cytopenia in 2 lineages; (3) splenomegaly; (4) elevated ferritin; (5) elevated triglycerides and/or reduced fibrinogen; (6) hemophagocytosis in bone marrow, spleen, or lymph nodes; (7) low or absent NK cell cytotoxic activity; and (8) elevated soluble CD25. Supporting evidence not required for diagnosis includes abnormal liver function tests, CNS involvement (based on clinical examination,

Table 3 Diagnostic and classification criteria for hemophagocytic lymphohistiocytosis

HLH2004 diagnostic criteria[a]	HScore diagnostic criteria[b]	Macrophage activation syndrome[c]
The diagnosis of HLH can be established by a molecular diagnosis consistent with HLH or by meeting ≥5 of the following 8 clinical and laboratory diagnostic criteria	A higher score is associated with a higher risk of HLH, as calculated based on the following criteria and scoring system	A patient with known or suspected systemic juvenile idiopathic arthritis is classified as having macrophage activation syndrome if the following criteria are met
(1) Fever	Temperature (°C): 0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)	Fever
(2) Ferritin ≥500 ng/ml	Ferritin (ng/ml): 0 (<2000), 35 (2000–6000), or 50 (>6000)	Ferritin >684 ng/ml
		Plus any 2 of the following
(3) Cytopenias (affecting ≥2 of 3 lineages in peripheral blood) Hemoglobin <90 g/l Platelets <100 × 10^9/l Neutrophils <1.0 × 109/l	Number of cytopenias (hemoglobin ≤9.2 gm/dl and/or leukocytes ≤5000/mm^3 and/or platelets ≤110,000/mm^3): 0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)	Platelets ≤181 × 10^9/l
(4) Splenomegaly	Organomegaly: 0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)	
(5) Hypertriglyceridemia and/or hypofibrinogenemia Fasting triglycerides ≥265 mg/dl Fibrinogen ≤150 mg/dl	Triglyceride (mg/dl): 0 (<132), 44 (132–353), or 64 (>353) Fibrinogen (mg/dl): 0 (>250) or 30 (≤250)	Triglycerides >156 mg/dl Fibrinogen ≤360 mg/dl
(6) Soluble CD25 ≥2400 U/ml	Serum glutamic oxaloacetic transaminase (IU/l): 0 (<30) or 19 (≥30)	Aspartate aminotransferase >48 U/l
(7) Low or absent NK cell activity	Known underlying immunosuppression due to human immunodeficiency virus or long-term immunosuppressive therapy: 0 (no) or 18 (yes)	
(8) Hemophagocytosis in bone marrow or spleen or lymph nodes	Hemophagocytosis features on bone marrow aspirate: 0 (no) or 35 (yes)	

Use US traditional units or equivalent values SI units

[a] Henter [91]

[b] In a development and validation study, the probability of having reactive hemophagocytic syndrome was <1 % with an HScore <90 to >99 % with an HScore >250; the median HScore for a positive diagnosis was 230 (IQR 203–257); and the median HScore for a negative diagnosis was 125 (IQR 91–150) [93]

[c] Ravelli et al. [140]

CSF findings, and/or CT or MRI scans), lymphadenopathy, rash, hyponatremia, and elevated LDH. Hence, a diagnosis is made by a constellation of clinicopathologic findings, familial history, or documentation of genetic mutations. The applicability of HLH-2004 criteria to adults with suspected HLH remains to be determined. Importantly, all of these features with the possible exception of splenomegaly can be found in severe SIRS secondary to trauma or sepsis [62]. Furthermore, the underlying predisposing conditions, such as rheumatologic disease or malignancy, may themselves affect baseline levels of some of these laboratory abnormalities. This clouds the issue of appropriate cutoffs and questions the use of specific criteria depending on the underlying disease.

A web-based, international Delphi study of 24 HLH experts identified 7 criteria as "absolutely required" or "important" for diagnosing sHLH in adults: cytopenia(s), demonstrable hemophagocytosis, fever, organomegaly, elevated ferritin, predisposing disease, and high LDH [92]. Four other criteria were of uncertain benefit: fibrinogen, triglycerides, elevated transaminases, and percentage of glycosylated ferritin. Fardet et al. [93] utilized the results of this Delphi study in a retrospective analysis of 312 patients to derive the HScore. This score included 6 of the "absolutely required" Delphi criteria, as well as 3 of 4 of uncertain benefit. Scores ranged from 0 to 337 with area under receiver operator curve of 0.97 in the original developmental data set and 0.95 in a separate validation set. The optimal cutoff was 169, accurately classifying 90 % of the patients. This scoring system is available online at http://saintantoine.aphp.fr/score/.

The use of HLH-2004 criteria to diagnose HLH (called MAS) in the setting of rheumatic disease is even more problematic. The cutoffs for thrombocytopenia, neutropenia, and fibrinogen in HLH-2004 may be too stringent for an autoinflammatory condition, such as sJIA where levels are typically high to start. More relevant may actually be a drop in these measurements. Ravelli et al. published guidelines for diagnosis of HLH in the setting of sJIA (Table 3) [94]. Laboratory criteria included (1) decreased platelet count ($\leq 262 \times 10^9$/l), (2) elevated aspartate aminotransferase (>59 U/l), (3) decreased WBC count ($\leq 4.0 \times 10^9$/l), and (4) hypofibrinogenemia ($\leq$250 mg/dl). Clinical criteria included (1) CNS dysfunction, (2) hemorrhages, and (3) hepatomegaly. Any 2 or more laboratory criteria or 2 or more laboratory and clinical criteria would be sufficient for diagnosis. The higher cutoffs compared to HLH-2004 for platelets, WBC count, and fibrinogen were required because of the elevated baseline levels. These criteria were recently validated in a large, retrospective, multinational study, with better performance compared to modified HLH-2004 criteria [95]. In another study of 27 patients with sJIA diagnosed with MAS by these guidelines, 33 % did not satisfy HLH-2004 criteria [96]. Similar issues apply to diagnosing MAS in AOSD and SLE, the 2 most common triggering autoimmune diseases in adults. In this situation, no specific diagnostic criteria have been published for adults.

If HLH is a consideration, the majority of criteria in either HLH-2004 or HScore are readily obtainable, with the exception of NK cell function and soluble CD25 levels. Of special note are serum ferritin and bone marrow aspiration (BMA). Unfortunately, neither is specific, and BMA lacks sensitivity. The pediatric HLH-2004 criteria use a ferritin cutoff of 500 ng/ml. Although quite sensitive, it is not specific, even in childhood. Allen et al. studied 330 consecutive children with maximum ferritin levels above 500 ng/ml. Only 10 were diagnosed with HLH. The optimal cutoff for diagnosing HLH in this retrospective pediatric cohort was 10,000 ng/ml with a sensitivity of 90 % and specificity of 96 % [97]. Adult series show even less specificity. Moore et al. studied 627 adult patients with maximum ferritin levels above 1000 ng/ml and found only 4 with HLH [98]. Beer et al. [99] studied 405 adult patients with ferritin levels above 5000 ng/ml and found only 3 cases had HLH. Schram et al. [100] evaluated 113 adult patients with ferritin levels above 50,000 ng/ml. HLH was found in only 19 (17 %), even at these extraordinarily high levels. Major contributing disorders to such hyperferritinemia in these series included renal failure, iron overload, hepatocellular injury, infection, and malignancy.

A bone marrow aspiration is mandatory to determine HPCs are present, as well as to rule out hematologic malignancy. The presence of HPCs on bone marrow aspiration is not required for diagnosis, however, as the sensitivity is only 60–85 % [101, 102]. Hence, a negative aspiration does not rule out HLH and should not delay specific treatment, if otherwise indicated [101]. Furthermore, finding HPCs is clearly not specific for HLH, as they can often be found following transfusions or surgery [103] and in the critically ill [7]. Suster et al. [104] studied 230 consecutive, autopsied adults and found moderate-to-severe HPCs in the bone marrow of 102 cases (44 %). This result was strongly associated with the number of recent RBC transfusions. In those with $\geq$5 units transfused, the adjusted odds ratio was nearly 60. Strauss et al. [7] studied 107 consecutive autopsied medical ICU patients and found hemophagocytosis in the bone marrow of 69 (64.5 %).

In all cases diagnosed as HLH, screening for genetic defects is recommended. If present, a decision regarding aggressive therapy and possible HSCT is simplified. Formal genetic testing is labor intensive and takes weeks to complete. Flow cytometric (FC) assays are available with results in several days. Normal degranulation of NK cells and CTLs results in surface expression of CD107a. Such expression is abnormal in FHL3-5 and the oculocutaneous

albinism syndromes, but normal in FHL2 and the XLP syndromes. FC staining for intracellular perforin is absent or greatly reduced in FHL2, and intracellular SAP and XIAP are deficient in XLP1 and 2, respectively. All patients should have CD107a and perforin assayed, and all male patients SAP and XIAP assayed as well [105]. Using this protocol, Bryceson et al. [106] evaluated 494 patients by FC with suspected HLH and found a sensitivity of 96 % and specificity of 88 % for differentiating genetic degranulation defects (FHL3-5 and oculocutaneous albinism syndromes) from FHL2, XLP1 and 2, and sHLH. Directed, formal genetic testing can then follow.

Identification of triggering agent

After establishing a diagnosis of HLH, it is imperative to search for a triggering agent that may require specific therapy [2, 105]. Malignancy and infection are the 2 most common triggers in adult HLH, with autoimmune disease a distant third [22–25]. The most common triggering infections are viral, especially EBV [45, 107] and other herpes viruses. Blood for PCR analysis should be obtained for EBV, CMV, VZV, herpes simplex, HHV6, HHV8, parvovirus B19, adenovirus, hepatitis, and influenza. Many other infections have been identified as triggering agents, especially intracellular pathogens, but also pyogenic bacteria [108]. If suspected, PCR of a bone marrow aspirate for leishmania should be performed. A malignancy evaluation is indicated in sHLH, especially in the absence of an identified infection or auto-inflammatory condition, and should include CT or MRI of chest and abdomen [109]. A bone marrow evaluation is mandatory, and a PET scan may also be considered.

Treatment of HLH

Treatment of HLH depends on the severity of hyperinflammation, underlying disease, the specific trigger, and whether or not an underlying genetic predisposition exists. No randomized, controlled treatment trials have been published, and only observational data exist. FHL in the pediatric age range is nearly uniformly fatal, with 1-year survival in early reports of less than 5 % [110]. The HLH-94 protocol of 8 weeks of dexamethasone and etoposide with intrathecal methotrexate in selected cases dramatically improved outcomes. In patients with persistent, familial, or relapsing disease, continued dexamethasone pulses, daily cyclosporine, and intermittent etoposide were used as a bridge to HSCT [55]. In a multinational series of 249 pediatric patients using this protocol, the estimated 5-year survival was 54 %, and this improved to 66 % in the 124 able to undergo HSCT [55]. Of note, 49 children were alive and well >1 year after completion of therapy that had a median duration of 4 months without HSCT. Presumably, these patients had sHLH. The HLH-2004 protocol added cyclosporine during the 8-week induction phase [91]. As an alternative regimen, a single-center series of 38 pediatric FHL patients received antithymocyte globulin (ATG) and methylprednisolone, along with intrathecal methotrexate and corticosteroids. Maintenance therapy then included cyclosporine and intermittent intravenous immunoglobulins until 26 eventually underwent HSCT [111]. The complete response rate to ATG was 73 % with another 24 % attaining a partial response. HSCT is indicated in patients with documented genetic mutations, as well as in those with familial, relapsing, or refractory disease. Reduced intensity conditioning appears to be better tolerated than myoablative conditioning.

The optimal treatment of sHLH in adults remains undefined. Although some cases resolve with just supportive therapy and treatment of the trigger, the most immediate issue is usually to quell the intense hyperinflammatory state. At a minimum for cases requiring urgent treatment, high-dose corticosteroids are indicated. In severe, familial, or relapsing disease, HLH-2004 should be considered. Etoposide appears to be especially suited for HLH, as it selectively deletes activated CD^{8+} CTLs in LCMV-infected $Prf^{-/-}$ mice and alleviates all manifestations of HLH [112]. Cyclophosphamide and methotrexate had similar effects, although other chemotherapeutic agents did not. In a retrospective analysis of 162 adults with sHLH, first-line use of etoposide was associated with significantly improved 30-day survival by multivariable analysis [113].

Treatment of an identified infectious trigger is mandatory, such as ganciclovir for CMV or amphotericin for leishmania. In the latter circumstance, antimicrobial therapy alone may suffice. In cases triggered by EBV, observational data support the use of etoposide in both pediatric [114] and young adult [115] patients. Treatment was most effective when instituted within 4 weeks of onset of disease [114, 115]. Theoretical support for use of etoposide derives from studies demonstrating EBV infection of CD^{8+} CTLs in EBV-HLH [116, 117]. Etoposide was also shown to have direct antiviral effects by inhibiting EBNA synthesis and EBV-induced transformation of mononuclear cells in vitro [118]. B cells may also be infected in EBV-HLH [119], and rituximab combined with traditional HLH therapy significantly reduced ferritin levels and EBV viral titers [120]. HSCT has also been effective in EBV-associated HLH [121].

Hyperferritinemic MODS in the ICU patient is not uncommon and merits consideration of sHLH. Such patients have severe SIRS caused by suspected/confirmed sepsis or a noninfectious illness, such as active

rheumatologic disease, catastrophic antiphospholipid syndrome, or trauma [26, 62]. Malignancy is also common [122, 123]. If sHLH is deemed present, the use of chemoimmunotherapy in a potentially septic patient, however, poses a dilemma. A family history of HLH or possibly consanguineous parents would necessitate the HLH-2004 protocol [124]. Rapid flow cytometric screening for genetic defects as outlined above should be performed, and if positive would also support HLH-2004 protocol, as would significant CNS involvement. Active malignancy would necessitate either HLH-2004 protocol or specific therapy.

Two recent series describe mortality and treatment of adult HLH cases admitted to the ICU, one based on HLH-2004 criteria [122] and one based on the HScore [123]. Hospital mortality ranged from 52 to 68 %, respectively. Steroids were used in 55 and 66 %, etoposide in 80 and 40 %, and intravenous immunoglobulin (IVIG) in 5 and 27 %, respectively. Some authors favor methylprednisolone over dexamethasone in ICU cases [125]. Plasma exchange (PE) and anakinra have also been employed. In a multicenter, retrospective cohort study of 23 critically ill children with hyperferritinemic syndrome, suspected sHLH was treated with PE and either IVIG or methylprednisolone ($n = 17$) and compared to PE and IVIG with dexamethasone, cyclosporine, or etoposide ($n = 6$). Despite documented infections in 15 patients, only 3 died, all receiving the more aggressive HLH-like agents [125]. Other data support the use of PE and IVIG [26, 62]. Anakinra appeared effective as initial therapy in a retrospective case series of 8 pediatric sHLH cases admitted to the ICU. However, 6 also received high-dose steroids, and 5 received IVIG [126]. Therapy was well tolerated, and anakinra is safe in patients with severe sepsis [127].

Recent series of adult HLH implicate malignancy as the most common trigger, usually lymphomas. HLH can complicate the active phase of malignancy or occur following chemotherapy-induced remission, where it is typically triggered by an infection [109, 128]. With active malignancy, it remains unclear whether first-line therapy should be HLH-directed (e.g., HLH-2004 protocol) or targeted to the specific malignancy. If HLH directed, specific malignancy therapy should immediately follow resolution of the hyperinflammation. Infection can also coexist with active malignancy, most notably EBV [129], and in such cases anti-B cell therapy is probably additionally indicated [109]. Active malignancy, usually lymphoma, is also found in over 50 % of HIV-associated HLH cases [130]. Chemotherapy-induced HLH results from infection and necessitates either reduction in intensity or interruption of further chemotherapy [109].

Mortality rates with HLH complicating auto-inflammatory/autoimmune diseases are generally much lower than with FHL or other causes of sHLH. Hence, initial therapy is less intense than HLH-2004 and usually does not include etoposide. For example, mortality in a large series of 362 HLH cases complicating sJIA was 8 % [131]. Nearly all (98 %) received corticosteroids, 61 % received cyclosporine, and 36 % received IVIG. Biologic agents were given to 15 %, most commonly anakinra (10 %), but also etanercept, rituximab, tocilizumab, infliximab, and canakinumab in a handful. Etoposide was only used in 12 %. Interestingly, HLH can develop in patients with sJIA undergoing treatment with biologic agents, including tocilizumab [132, 133], canakinumab [134], and anakinra [135]. In the latter case, dose escalation was effective in treatment [135]. In juvenile lupus-associated HLH, mortality is around 10 % [39], with steroids (100 %), cyclosporine (38 %), and IVIG (32 %) being the mainstays of therapy in a multicenter series and literature review of 38 patients [39]. The largest series of adult autoimmune/autoinflammatory HLH in the absence of coexisting active infection or malignancy reported 116 patients, including 61 with SLE and 31 with AOSD. Overall mortality was 13 %. Corticosteroids were used in 98 %, with 53 % of 87 patients responding to steroid monotherapy [38]; however, IVIG was used in 24 %, cyclosporine in 21 %, IV cyclophosphamide in 15 %, and etoposide in only 3 %. In the presence of an infectious trigger, and in the absence of an underlying disease flare, reduction in immunosuppression may be preferred in SLE-associated HLH [40].

Little data exist to guide therapy of HLH in kidney transplant recipients. As shown above, the vast majority of cases are triggered by infections, which should be specifically treated whenever possible. We believe calcineurin inhibitor therapy should be continued given the role of cyclosporine in HLH-2004. High-dose steroids are indicated, and antimetabolite therapy should be discontinued to reduce possible over-immunosuppression. If rejection develops, IVIG is a consideration, with PE if antibody mediated. If EBV is detected, dexamethasone, etoposide, and rituximab seem justifiable.

Conclusion

Nephrologists need to be aware of the clinical manifestations, diagnosis, and treatment of HLH in its various settings. In the acutely ill ICU patient with AKI in the setting of MODS, HLH may have supervened, a situation necessitating specific treatment. Similarly, patients with autoimmune and autoinflammatory diseases may develop HLH and present with glomerulopathy associated with the either the underlying disease or HLH. Finally, in immunosuppressed kidney transplant patients, when clinical conditions suggest it, HLH must be recognized as mortality is over 50 %.

Compliance with ethical standards

Conflict of interest EJF: speaker's bureau for Mallinckrodt Pharmaceuticals; JLF: none.

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