CME/SAM

Extreme Hyperferritinemia

Causes and Impact on Diagnostic Reasoning

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ABSTRACT

Objectives: *Hyperferritinemia can be a result of inflammation, infection, chronic iron overload, or other uncommon pathologies including hemophagocytic lymphohistiocytosis (HLH). There is a historical association between extreme hyperferritinemia and HLH, but in reality HLH is associated with a minority of hyperferritinemic states.*

Methods: *We identified conditions most associated with hyperferritinemia by identifying 65,536 serum ferritin levels at the University of Minnesota Hospital over a five-year period, with 86 values higher than 10,000 ng/mL. Pediatric patients comprised 22% of this population, and adults, 78%.*

Results: *The majority of cases in both populations with hyperferritinemia were due to chronic transfusion (35%), followed by liver disease (27%), and hematologic malignancy (16%). Solid malignancies, infection, macrophage activation syndrome, and primary and secondary HLH comprised the remaining (22%).*

Conclusions: *Although this supports the relationship between extreme hyperferritinemia and HLH, it maintains that the positive predictive value of hyperferritinemia for HLH is quite low, and one should consider more common explanations before suspecting HLH.*

Upon completion of this activity you will be able to:
- describe ferritin's normal physiologic function.
- name the eight diagnostic criteria used to identify hemophagocytic lymphohistiocytosis.
- identify common and uncommon conditions that can be associated with hyperferritinemia.

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Ferritin is a molecule that has many roles, ranging from the binding and storage of iron to contributing to inflammation, cell signaling and immune function.[1] The normal range of serum ferritin is gender and age specific, 7 to 10 ng/mL for infants and 20 to 300 ng/mL for adults. Elevations in serum ferritin have been observed in common conditions, including sepsis due to bacterial, fungal or viral sources, or iron overload due to hemochromatosis or chronic transfusions, or as a general marker of inflammation.[2,3] The magnitude of elevation in serum ferritin has been linked with worse prognosis.[4] Serum ferritin levels can occasionally reach extremes greater than 10,000 ng/mL. Classically, a very limited differential diagnosis has been considered for patients with such extreme hyperferritemia, including sepsis, infection (especially fungal), and iron overload, and rare causes such as hemophagocytic lymphohistocytosis (HLH).[5,6]

Hemophagocytic lymphohistiocytosis can be divided into two types, familial (fHLH) and secondary (sHLH). fHLH is an autosomal recessive condition that typically presents in early infancy and is fatal unless treated. sHLH is thought to result from a strong activation of the immune system, often caused by infection. The diagnostic criteria for HLH must include five of these eight findings: hyperferritinemia, fever, splenomegaly, bicytopenia, elevated triglycerides and/or decreased fibrinogen, hemophagocytosis identified (usually in a bone marrow, liver or lymph node specimen), decreased or absent NK cell function, and increased soluble IL-2 receptor.[7] Despite the fact that HLH is rare and multiple recent articles have suggested that the positive predictive value of extreme hyperferritemia is poor, clinicians still have a reflexive association between extreme hyperferritinemia (levels >10,000 ng/mL) and HLH in their diagnostic reasoning. Our primary aim was to determine the primary clinical cause of extreme hyperferritinemia in a tertiary care population over a five-year period.

Materials and Methods

With Institutional Review Board (IRB) approval, all serum ferritin values measured at the University of Minnesota Medical Center laboratory between February 1, 2007, and February 23, 2012, were imported from the medical records system database into a Microsoft Excel data file for further analysis. Serum ferritin evaluations in our institution are performed using a two-site chemiluminescent immunoassay (Vista Centaur; Siemens, Erlangen, Germany). The patients with any single measurement greater than 10,000 ng/mL were identified and selected for the study. The patient medical record charts were reviewed and the primary diagnosis was determined by the authors' expert review. Based on the authors' review, diagnoses were classified into the following categories: "Chronic Transfusion," "Liver Disease," "Malignancy—Hematologic," "Malignancy–Solid," "Hemoglobinopathy," "Infection—Bacterial," "Infection—Fungal," "Infection–Viral," "Infection—Other," "Primary HLH," "Secondary HLH," "Macrophage Activation Syndrome," and "Diagnosis Not Determined." HLH-2004 criteria as defined by Henter et al[7] were used for the determination of HLH diagnosis. Patients were categorized as adult if their age was greater than 18 years on the date of the ferritin value measurement.

Results

There were 269 values (0.4%) over 10,000 ng/mL in 86 unique patients ranging from 10,006 ng/mL to 143,931 ng/mL. The population was comprised of 19 pediatric patients (22%), with the remaining 67 patients being adults (78%). The primary diagnosis in the majority of cases in both the pediatric and adult populations with hyperferritinemia was iron overload from chronic transfusions (35% total, 37% pediatric, 34% adult). This was followed by liver disease (27% total, 11% pediatric, 31% adult), and hematologic malignancies (16% total, 21% pediatric, 15% adult). Solid malignancies were associated with hyperferritinemia in 2% of overall cases, 3% of adult cases, and none of the pediatric cases. Primary HLH affected 11% of the pediatric population and only 1% of the adult population (3% overall). In the adult population, sHLH comprised 7% of cases of hyperferritinemia (6% of all subjects), but was not seen in any of the hyperferritinemia cases in children. Overall, bacterial, fungal, and viral infections accounted for 3%, 1% and 2% of overall cases, respectively. Bacterial, fungal, and viral infections were associated with hyperferritinemia in adults in 3%, 1%, and 0%, respectively; in children, 5% of cases were associated with bacterial infection, 11% with viral infections, and no cases were associated with fungal infection. One adult patient had hyperferritinemia associated with a *Babesia* infection, categorized as "Infection–Other," and comprised 1% of the adult and overall population of this subset. Hemoglobinopathy was seen in 1% of hyperferritinemia cases overall and in the adult population, but not in any of the cases of pediatric hyperferritinemia. The cause of the hyperferritinemia was unable to be determined in 6% of pediatric (and 1% in overall) cases **Table 1**. To further characterize the cases of hyperferritinemia associated with liver disease, patients classified into this category were divided according to whether they had either an acute or a chronic

Table 1
Percentage of Conditions Associated With Hyperferritinemia[a]

	Adult	Child	Overall
Chronic Transfusion	34% (23)	37% (7)	35% (30)
Liver Disease	31% (21)	11% (2)	27% (23)
Malignancy—Hematologic	15% (10)	21% (4)	16% (14)
Malignancy—Solid	3% (2)	0% (0)	2% (2)
Hemoglobinopathy	1% (1)	0% (0)	1% (1)
Infection—Bacterial	3% (2)	5% (1)	3% (3)
Infection—Viral	0% (0)	11% (2)	2% (2)
Infection—Fungal	1% (1)	0% (0)	1% (1)
Primary HLH	1% (1)	11% (2)	3% (3)
Secondary HLH	7% (5)	0% (0)	6% (5)
Infection—Other (*Babesia*)	1% (1)	0% (0)	1% (1)
Diagnosis Not Determined	0% (0)	5% (1)	1% (1)
Total	100% (67)	100% (19)	100% (86)

HLH, hemophagocytic lymphohistiocytosis.
[a]The majority of conditions associated with hyperferritinemia were chronic transfusion, followed by hematologic malignancy, liver disease (acute and chronic), with 11% or less associated with solid malignancies, hemoglobinopathy, infections, HLH and diagnosis not determined. Data are given as percent (No. of patients).

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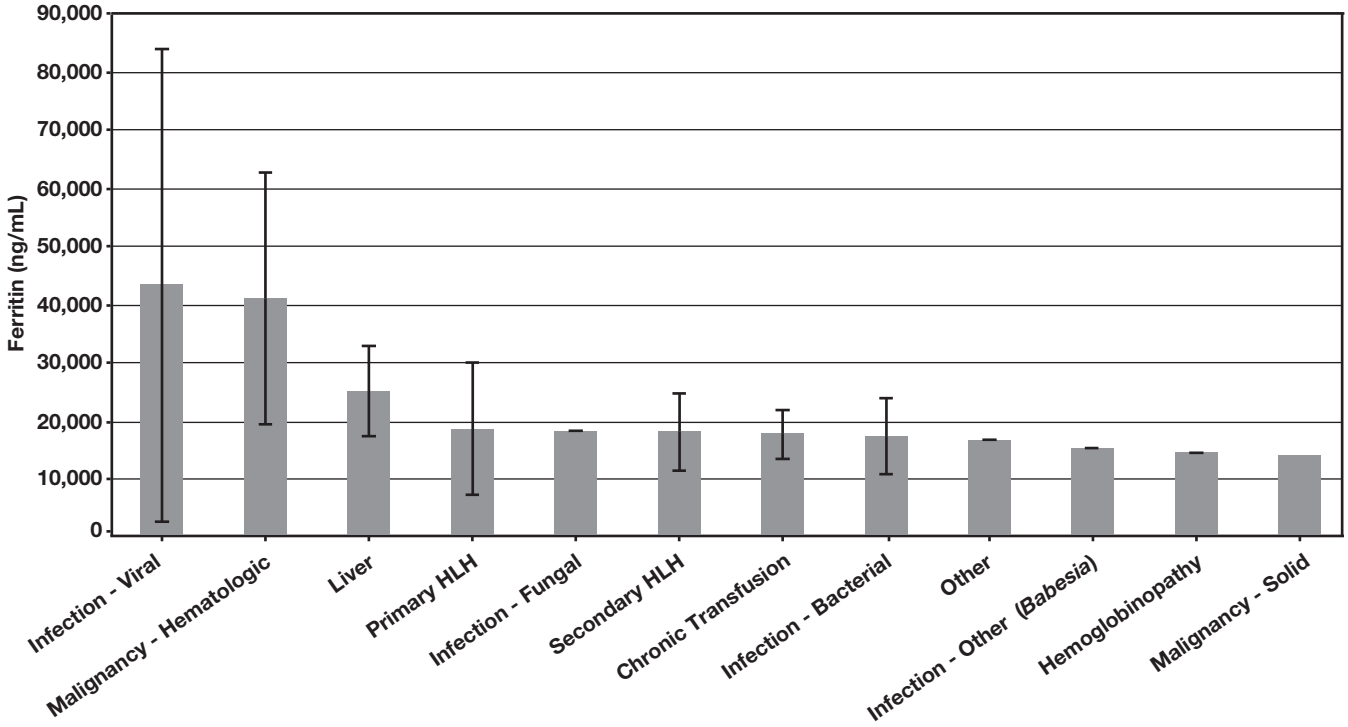

Figure 1 Average serum ferritin by condition. The average ferritin value for each diagnosis is displayed in the descending order along with the error bars indicating 95% confidence interval computed using normal distribution. HLH, hemophagocytic lymphohistiocytosis.

hepatic disease. Of the 27% of those patients with liver disease, 16% overall (14 patients) had chronic liver disease; none were pediatric patients. Of those with acute liver disease associated with hyperferritinemia, 11% overall (nine patients) had acute liver disease, with 10% (seven) being adults, and 11% (two) being children. The primary diagnosis associated with hyperferritinemia that displayed the widest range of ferritin values was hematologic malignancy, with a range from 10,036 ng/mL to 143,931 ng/mL **Figure 1** and **Table 2**. Cases of hematologic malignancy had the highest serum ferritin values: the only two ferritin values over 100,000 ng/mL (115,967 ng/mL and 143,931 ng/mL). Patients with hyperferritinemia associated with chronic transfusion displayed ferritin ranges from 10,006 ng/mL to 54,087 ng/mL. Those with hyperferritinemia associated with liver disease showed a range from 10,877 ng/mL to 93,103 ng/mL. Hyperferritinemia associated with solid malignancy displayed a range from 13,613 ng/mL to 14,754 ng/mL. The one patient with hyperferritinemia associated with a hemoglobinopathy had a ferritin value of 14,526 ng/mL. Bacterial, viral and fungal infections displayed ranges from 11,300 ng/mL to 25,460 ng/mL, 14,037 ng/mL to 72,710 ng/mL and 18,349 (one patient), respectively. Primary HLH displayed a range from 10,214 ng/mL to 33,000 ng/mL, while sHLH ranged from 10,548 ng/mL to 27,880 ng/mL. The final two patients, one with a *Babesia* infection associated with hyperferritinemia (classified as "Infection—Other") and another with an unknown cause of hyperferritinemia displayed serum ferritin values of 15,219 ng/mL and 16,808 ng/mL, respectively (see Table 2 and Figure 1). The ANOVA analysis revealed no statistical difference among the serum ferritin means for each diagnosis ($P = .31$). The distribution of ferritin values across ranges is shown in **Table 3**.

Discussion

Extreme hyperferritinemia (defined as a ferritin level >10,000 ng/mL) often triggers a thought process that includes many rare and serious differential diagnoses such as HLH, while more common disorders are dismissed.[8,9] This may be due to incompletely developed illness scripts for both hyperferritinemia and HLH, and clinicians' utilization of the availability heuristic, in which disorders that are more "available" in a clinician's mind are more likely to be considered.[4] HLH is an uncommon disorder that affects approximately 1:50,000 patients per year.[10] Although the hallmark sign of HLH is hyperferritinemia, our study shows that a very high ferritin level may be sensitive for a diagnosis of HLH, but has a very poor positive predictive value. Instead, common clinical conditions, including liver disease, iron overload and malignancy are much more likely in patients with hyperferritinemia.[11]

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Table 2
Conditions Associated With Hyperferritinemia With Range[a]

Diagnosis	n	Ferritin Range (ng/mL)	Mean (ng/mL)	95% CI (ng/mL)
Chronic Transfusion	30	10,006-54,087	17,669	13,519-21,819
Liver Disease	23	10,877-93,103	25,161	17,278-33,043
Malignancy—Hematologic	14	10,036-143,931	41,109	19,382-62,836
Solid Malignancy	2	13,613-14,754	14,184	13,393-14,974
Hemoglobinopathy	1	14,526	14,526	–
Infection–Bacterial	3	11,300-25,460	17,430	10,715-24,146
Infection–Viral	2	14,037-72,710	43,374	2,716-84,031
Infection–Fungal	1	18,349	18,349	–
Primary HLH	3	10,214-33,000	18,806	7,365-30,247
Secondary HLH	5	10,548-27,880	18,200	11,503-24,897
Infection—Other (*Babesia*)	1	15,219	15,219	–
Diagnosis Not Determined	1	16,808	16,808	–

[a]The range of ferritin values within each diagnosis is displayed, along with the number of patients that were assigned the respective diagnosis as "primary." The largest range of values is seen in the "Malignancy—Hematologic" diagnosis, which also contains the highest ferritin value identified, of 143,931 ng/mL.

Table 3
Number of Patients With Hyperferritinemia Within Each Range of Serum Ferritin[a]

Ferritin (ng/mL)	n
10,000-19,999	53
20,000-29,999	19
30,000-39,999	3
40,000-49,999	2
50,000-59,999	2
60,000-69,999	2
70,000-79,999	1
80,000-89,999	1
90,000-99,999	1
>100,000	2

[a]The number of patients with ferritin values within each range, with the largest number of patients with hyperferritinemia between 10,000 ng/mL and 19,999 ng/mL.

While a high index of suspicion is necessary to avoid missing rare diagnoses, care must be taken to avoid overtesting and overdiagnosis of HLH based on serum ferritin levels alone. Treatment of HLH often involves administration of cytotoxic chemotherapy, and thus a high diagnostic threshold must be used, given the potential for side effects and complications stemming from treatment.[12,13] The approach to a patient with hyperferritinemia should encompass not only the rarer entities described above, but should also include the more common and seemingly mundane differentials of infection and iron overload. Our results show that of the 65,536 ferritin levels that were drawn over the course of five years, less than 1% showed extreme hyperferritinemia. It should be noted that this sample population is taken from a tertiary care center, so the incidence of less than 1% may be even smaller in other populations. This is consistent with other case studies, showing prevalence of extreme hyperferritinemia to be 0.08%.[2] In our study, 11% of pediatric cases, 1% of adult cases and 3% of overall cases of hyperferritinemia were associated with HLH. A large proportion of hyperferritinemic states were due to chronic transfusion and malignancies. The University of Minnesota has a robust bone marrow transplantation program, and thus such diagnoses may be overrepresented compared to other populations. The percentage of total patients who had hyperferritinemia associated with viral, bacterial, or fungal infections (2%, 3%, and 1%, respectively) is likely consistent with other populations. Patients who had hyperferritinemia associated with chronic transfusions (30 in total) had serum ferritin values that fell in the lower half of the hyperferritinemic range (<59,000 ng/mL), while the remaining diagnoses displayed a wider range of ferritin values. Patients with hyperferritinemia associated with a hematologic malignancy displayed not only the widest range of serum ferritin values (10,036 ng/mL to 143,931 ng/mL), but also boasted the highest ferritin values, with the two ranges that were greater than 100,000 ng/mL. The majority of cases with hyperferritinemia showed values that were lower than 19,999 ng/mL (53 patients), and the remaining 33 patients had ferritin values between 20,000 ng/mL and just over 100,000 ng/mL. This is also consistent with other literature that shows the majority of hyperferritinemia cases have values that range in the 10,000 ng/mL to approximately 50,000 ng/mL, with fewer cases reaching serum ferritin values higher than 50,000 ng/mL.[2]

There were limitations to our study. First, this was a retrospective chart review study, and diagnoses were drawn from clinical documentation and may be subject to error. In addition, there may be local institutional and epidemiological characteristics that make the data less generalizable: for example, the one case of hyperferritinemia associated with a *Babesia* infection may be less geographically generalizable, as this parasite is more endemic in geographic locations such as the Midwest and Northeast.[14]

Our study shows that the prevalence of HLH in patients with extreme hyperferritemia is very low and that an extremely elevated ferritin level has a poor positive predictive value for HLH. Clinicians should not be blindly obedient to

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a lab value; rather one should evaluate the evidence and consider what is common when diagnosing patients with hyperferritinemia.

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