Causes and Significance of Markedly Elevated Serum Ferritin Levels in an Academic Medical Center

Charles Moore, Jr, MD, Michelle Ormseth, MD, and Howard Fuchs, MD

Objective: A markedly elevated serum ferritin level has been associated with inflammatory conditions such as adult-onset Still's disease, systemic juvenile idiopathic arthritis, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Hyperferritinemia, however, can also be caused by a wide variety of disparate conditions, often with impressively high serum levels. The objective of this analysis was to investigate the underlying etiology of markedly elevated ferritin levels in a large group of patients treated as outpatients and inpatients in a tertiary-care medical center.

Methods: Data of all adult patients from 2008 through 2010 with at least 1 serum ferritin level greater than 1000 μg/L were reviewed. If a patient had multiple qualifying levels, the highest one was used. For each case, the most likely cause of the elevated ferritin was assessed based on the available clinical data using a simple algorithmic approach.

Results: Six hundred twenty-seven patients were found. The average serum ferritin level was 2647 μg/L. The most frequent condition was malignancy (153/627), with iron-overload syndromes the second most common (136/627). There were 6 cases of adult-onset Still's disease, systemic juvenile idiopathic arthritis, or hemophagocytic lymphohistiocytosis/macrophage activation syndrome. The average ferritin level in these syndromes was 14242 μg/L. Seven patients appeared to have anemia of chronic inflammation, and in 5 patients, there was no clearly definable cause for hyperferritinemia.

Conclusions: Although extremely elevated ferritin levels may be associated with rheumatologic diseases, more often they are found in patients with other conditions such as malignancy or infection. In addition, extremely high ferritin levels can be found in patients with seemingly indolent disease or levels of chronic inflammation.

Key Words: ferritin, hemophagocytic lymphohistiocytosis, adult-onset Still's disease, systemic juvenile rheumatoid arthritis, macrophage activation syndrome

(*J Clin Rheumatol* 2013;19: 324–328)

Ferritin is a 24-subunit evolutionarily conserved protein. Within the cytosol, its main function is to store iron in a soluble nontoxic form, protecting the cell from iron-mediated oxidation-reduction reactions. In the circulation, it acts as a delivery mechanism, and serum levels usually reflect total body iron stores.[1] It can be abnormally elevated in a wide range of disease states including malignancy, infection, inflammation, and chronic iron-overload syndromes. Previous investigators have examined the underlying causes of markedly elevated ferritin levels. Liver disease, malignancy, and renal disease have been found to be prominent causes,[2] and infections predominated in a recent HIV-positive cohort.[3]

Rheumatologists are often asked to evaluate patients with markedly elevated serum ferritin levels because of the role it plays as an acute-phase reactant and because of the long-standing association between markedly elevated ferritin levels and rheumatologic diseases such as adult-onset Still's disease (AOSD)[4] or systemic-onset juvenile idiopathic arthritis (SJIA).[5] However, making a definitive diagnostic link between a markedly elevated serum ferritin determination and a specific diagnosis, rheumatologic or otherwise, can be challenging as the manifestations of these diseases are often protean and can easily be mistaken for other conditions such as sepsis with multiple organ failure or malignancy.

We reviewed the charts of adult patients with serum ferritin levels greater than 1000 μg/L. We chose this number because it allows for broad clinical applicability in a wide range of patients with hyperferritinemia. These patients were then categorized into specific syndromes known to cause marked hyperferritinemia. We hypothesized that our results would differ from previous studies because of the low prevalence of HIV in our patient population. In addition, over the past several years, there has been an increased appreciation of the association of hemophagocytic lymphohistiocytosis (HLH) with marked hyperferritinemia as well as increased recognition of secondary HLH or macrophage activation syndrome (MAS), in patients with a wide range of primary inflammatory, malignant, and infectious syndromes.[6]

MATERIALS AND METHODS

Serum ferritin evaluations in our institution are performed using a 2-site immunoenzymatic assay (Beckman Coulter, Brea, CA). Our local clinical laboratory considers a normal serum ferritin to be 30 to 270 μg/L and does not account for patient gender. Our electronic medical record was queried for serum ferritin values greater than or equal to 1000 μg/L occurring from January 1, 2008, through December 31, 2010. The search was limited to patients 18 years or older. For patients having multiple ferritin levels greater than 1000 μg/L, the highest value was used. When available, serum iron and total iron-binding capacity (TIBC) within 30 days of the index ferritin level were recorded, as were erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) if done within 14 days. Each patient's chart was reviewed, and the most likely cause of hyperferritinemia was decided based on available clinical data. In patients having more than 1 possible etiology, a single predominant underlying cause was decided using a simple algorithm (Fig. 1).

Patients categorized as having iron overload had had monthly red blood cell transfusions for at least 6 months, had been clinically judged to be iron-overloaded by a hematologist, and/or were receiving iron chelation therapy in the setting of a known iron-overload syndrome.

From the Division of Rheumatology and Immunology, Vanderbilt University Medical Center, Nashville, TN.
This study has no sources of support.
The authors declare no conflict of interest.
Reprints: Howard Fuchs, MD, Division of Rheumatology and Immunology, Vanderbilt University Medical Center, S-3113 MCN, Nashville, TN 37232.
Correspondence: Charles Moore, Jr, MD, Division of Rheumatology and Immunology, Vanderbilt University Medical Center, S-3113 MCN, Nashville, TN 37232. E-mail: Charles.f.moore.1@vanderbilt.edu.

ISSN: 1076-1608/13/1906–0324
DOI: 10.1097/RHU.0b013e31829ce01f

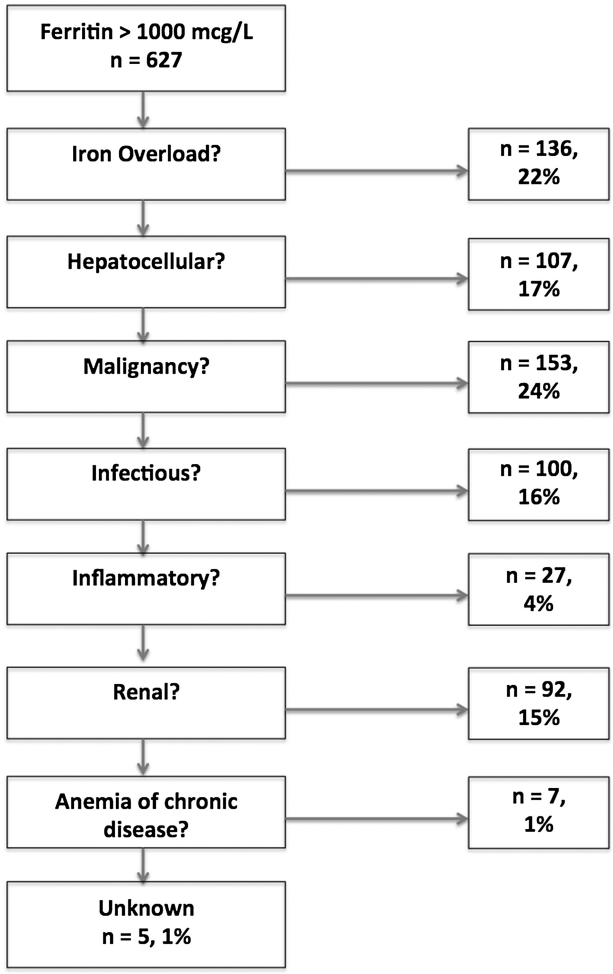

FIGURE 1. Priority of categorizing subjects and prevalence of each category.

Hepatocellular causes for hyperferritinemia included alcoholic liver disease, active hepatitis B or C infection, cirrhosis (due to nonalcoholic steatohepatitis, primary biliary cirrhosis), autoimmune hepatitis, severe graft-versus-host disease involving primarily the liver, and liver failure due to transient hypotension, toxic ingestion, or graft failure after orthotopic liver transplant. Hyperferritinemia due to severe sepsis or multiple organ dysfunction was classified in this category if hepatic involvement clinically predominated.

Patients were classified as having malignancy if their cancer was active or untreated, or if they were receiving therapy but were within 6 months of their cancer diagnosis. Hematologic malignancies predominated and included myeloma, angioblastic T-cell lymphoma, Hodgkin disease, diffuse large B-cell lymphoma, and mantle cell lymphoma. The most common solid malignancies diagnosed included liver, lung, thyroid, esophageal, breast, renal, pancreatic, colon, and prostate cancers.

Inflammatory causes of hyperferritinemia were composed of those known to be particularly associated with markedly elevated serum ferritin levels (HLH/MAS, Still's disease) as well as those associated with chronic inflammation. These included flares of systemic lupus erythematosus and flares of granulomatosis with polyangiitis, as well as active rheumatoid arthritis, scleroderma with pericarditis, flare of inflammatory bowel disease, and active graft-versus-host disease. Patients with iron indices consistent with anemia of chronic disease (normocytic anemia and low TIBC) and no other apparent etiology for their elevated ferritin were placed in the separate category of anemia of chronic disease. In addition, patients who were judged by a hematologist to have anemia of chronic disease were also labeled as such.

For the purposes of categorization, possible infectious causes of a markedly elevated ferritin level had to be either acute and severe (ie, requiring inpatient admission and/or aggressive antibiotic therapy) or chronic in nature, requiring long-term antibiotics and/or surgical debridement. Several patients met criteria for SIRS (systemic inflammatory response syndrome), but no infectious source was isolated. These patients were classified in the infectious category based on the treating physician's clinical judgment that they were, in fact, septic.

Patients placed in the category of chronic kidney disease had to have a documented glomerular filtration rate less than 20 mL/min per 1.73 m^2, have stage 4 or 5 chronic kidney disease as assessed by a nephrologist, be on renal replacement therapy, or have chronic kidney disease and be within 3 months of starting renal replacement therapy.

Descriptive statistics were calculated as mean (SD) for continuous variables, and frequency and proportions for categorized values. Wilcoxon rank sum tests were used to compare continuous variables, and Pearson χ^2 or likelihood ratio tests were used to compare categorical variables. Statistical analyses were performed using IBM SPSS Statistics, version 20.0 (SPSS Inc, Chicago, IL). Two-sided $P \leq 0.05$ was considered statistically significant.

RESULTS

A total of 627 adult patients had a serum ferritin level of at least 1000 μg/L during the study period. Sixty-three percent were white, and 26% were black or African American. There was an overall male preponderance (57.3%). Patient ages ranged from 18 to 91 years (Table 1). The most frequent overall underlying cause of hyperferritinemia was malignancy (24%), with iron-overload syndromes the second most common (22%) (Fig. 1). There were relatively few cases due to purely inflammatory syndromes (n = 27, 4.3%), and of these, only 6 cases due to HLH/MAS or Still's disease. In 5 cases, no obvious underlying cause could be ascertained. Men often have higher ferritin levels than do women, but when analyzed separately, there were no significant differences between genders in the apparent cause of hyperferritinemia ($P > 0.4$). In patients younger than 50 years of age, the most common cause was iron overload (27.8%), followed by hepatocellular causes (18%). In patients older than 50 years, malignancy was the dominant cause (30.1%)

TABLE 1. Subject Demographics

Age, y	Range	18–91
	Median	55
	Mean	54
Gender, n (%)	Male	268 (42.7)
	Female	359 (57.3)
Race, n (%)	White	393 (63)
	Black/African American	162 (25.8)
	Asian	9 (1.4)
	Hispanic	3 (0.5)
	Other	33 (5.3)
	Unknown	27 (4.3)

TABLE 2. Prevalence of Each Category by Age

	n (%)
<50 y old	
Iron overload	68 (30)
Hepatocellular	41 (18)
Infectious	38 (16.7)
Renal failure/insufficiency	34 (14.9)
Malignancy	33 (14.5)
Inflammatory	10 (4.4)
Anemia of chronic disease	2 (0.9)
Unknown	2 (0.9)
≥50 y old	
Malignancy	120 (30.1)
Iron overload	68 (17)
Hepatocellular	66 (16.5)
Infectious	62 (15.5)
Renal failure/insufficiency	58 (14.5)
Inflammatory	17 (4.3)
Anemia of chronic disease	5 (1.3)
Unknown	3 (0.8)

followed by iron overload (17%) and hepatocellular disease (16.5%) (Table 2).

The mean (SD) serum ferritin level across all categories was 2647 (SD, 3771) μg/L. The highest mean ferritin level was seen in the inflammatory syndromes (4799 [SD, 6830] μg/L), with iron-overload–associated disease the second highest (3112 [SD, 3289] μg/L). The category of anemia of chronic disease had the lowest mean ferritin (1248 [SD, 155] μg/L), whereas those patients with chronic kidney disease had the second lowest (1580 [SD, 1046] μg/L) (Table 3).

Data on serum iron and TIBC were available for 352 subjects, allowing for calculation of transferrin saturation. As expected, the highest mean transferrin saturation was found in the iron-overload category (50% saturation). The lowest transferring saturation was seen in patients with anemia of chronic disease (18.9% saturation) and patients with infections (24% saturation).

There were 18 patients with serum ferritin levels greater than 10,000 μg/L. Within this subgroup, there were 6 patients with a malignancy, 4 with an iron-overload syndrome, 4 with an inflammatory etiology, and 2 each with an infectious or hepatocellular cause.

There were 4 cases of HLH/MAS. Three of these were confirmed by bone marrow biopsy. In the fourth, the diagnosis was made on clinical grounds as bone marrow biopsy was nondiagnostic. Acute infection with *Escherichia coli* was the triggering factor in 1 case. Another arose in the setting of T-cell lymphoma. The remainder were idiopathic. Cases of AOSD/SJIA were diagnosed clinically using the preliminary criteria of Yamaguchi et al.[7] There was 1 case of AOSD (2 major criteria, 3 minor) and 1 adult patient with a history of SJIA (2 major criteria, 2 minor). When analyzed separately, patients with the diagnosis of HLH/MAS/SJIA/AOSD had significantly higher serum ferritin determinations than the overall mean (14,242 [SD, 9379] vs 2535 [SD, 3512], $P < 0.001$) and in those with other inflammatory conditions (14,242 [SD, 9379] vs 2101 [SD, 2064], $P < 0.001$) (Fig. 2).

Five patients had no clear diagnosis to explain their hyperferritinemia. A 64-year-old man with a yearlong history of recurrent fever and weight loss was admitted with liver failure, renal failure, and pancytopenia. His ferritin was 5766 μg/L. He underwent an extensive workup, which failed to uncover a unifying diagnosis. He was not evaluated by a rheumatologist. A 30-year-old man presented with recurrent fever, bilateral pleural effusions, and a serum ferritin of 1505 μg/L. He also underwent an extensive evaluation, including rheumatology consultation, without a clear diagnosis being found.

Three patients with no apparent etiology for hyperferritinemia had no clinical illness and appeared well. The mean serum ferritin in this group was 2132 (SD, 912) μg/L. All 3 were previous transplant recipients (2 renal, 1 renal/pancreas) with normal graft function, and all 3 were chronically immunosuppressed. Acute-phase reactants were unavailable for all 3, and iron indices were not consistent with anemia of chronic inflammation.

TABLE 3. Mean (SD) for Each Diagnostic Category

	Mean, μg/L	SD
Anemia of chronic disease	1248.4	155
Hepatocellular	2477.4	4866
Severe infection	2408.8	3134
Inflammation	4799.2	6830
Iron overload	3112.3	3289
Malignancy	2849.9	3926
Renal failure/insufficiency	1580.6	1046
Unknown	2132	2039

DISCUSSION

Serum ferritin level is a nonspecific indicator of systemic illness and can be elevated through a variety of mechanisms, which may overlap or coexist. Systemic inflammation plays a key role in the initiation and perpetuation of hyperferritinemia. Serum ferritin has been widely accepted as an acute-phase reactant and is nonspecifically elevated in a wide variety of inflammatory states including infection, malignancy, and autoimmune diseases. It is particularly elevated in cases of AOSD and HLH, and in fact, the diagnosis of both syndromes rests partially on the presence of a markedly elevated serum ferritin level.[7] Diagnostic criteria for HLH include a serum ferritin level greater than 500 μg/L as a minor criterion,[8] and an elevated serum ferritin level is seen in approximately 90% of patients with AOSD/SJIA.[9] In both of these syndromes, serum ferritin levels

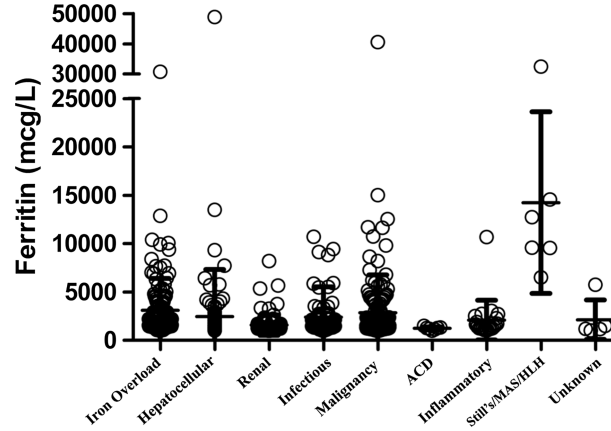

FIGURE 2. Mean (SD) ferritin (in μg/L). Still's disease and MAS/HLH have been analyzed separately.

can exceed 20,000 μg/L.[10] Several groups have established a role for glycosylated ferritin in the diagnosis of inflammatory causes of hyperferritinemia. Fardet et al.[11] found significantly lower levels of glycosylated ferritin in patients with hemophagocytic syndrome, and Fautrel et al.[12] found that diagnostic criteria for AOSD, which included a glycosylated ferritin fraction of 20% or less, resulted in improved sensitivity and specificity. This assay, however, is as yet not widely used or available, and glycosylated ferritin levels were not available to us in this analysis.

Serum ferritin and systemic iron handling are affected by inflammatory pathways involving the up-regulation of hepcidin. Ferroportin is a cellular membrane protein that allows the egress of iron from enterocytes into the circulation. It is present as well on cells of the reticuloendothelial system, particularly macrophages. Hepcidin binds to and inactivates ferroportin, causing its internalization and degradation within the cell, the net effect of which is to decrease iron absorption from the gut and to limit the amount of iron made available to the circulation, sequestering iron within the reticuloendothelial system.[13] Hepcidin production within the liver is stimulated by proinflammatory cytokines, particularly IL-6,[14] and it is this constellation of findings (decreased serum iron, increased ferritin, and increased hepcidin levels) that is seen in anemia of chronic inflammation. It is likely that this mechanism at least partially underlies the hyperferritinemia seen in patients with chronic infections, chronic kidney disease, autoimmune disease, and malignancies.

In our patient population, there were very few patients with HLH/MAS or AOSD/SJIA. This may attest to the relative rarity of these diseases, even in a large tertiary medical center. The ferritin cutoff of 1000 μg/L was chosen based on previous work showing that a cutoff of greater than 5 times the upper limit of normal is suggestive of AOSD,[15] but it is possible that this value was too high to pick up more of these patients. For example, in a Japanese cohort of patients with AOSD, 6 of 34 patients had normal ferritin levels, and 6 patients with elevated hyperferritinemia had levels less than 5 times the upper limit of normal.[16] Although our patients with established Still's disease or HLH/MAS had markedly elevated serum ferritin levels as one would expect, many more patients with extreme hyperferritinemia had an alternative diagnosis, such as malignancy or infection.

Five of our patients we were unable to clearly categorize. Three of these had undergone solid organ transplantation and were receiving chronic immune suppressive therapy. Although all 3 had normal graft function, it is possible that they all had some level of chronic inflammation, which would account for their elevated serum ferritin level. Iron indices and acute-phase reactants in these patients either were not available or were not indicative of anemia of chronic inflammation. There are data in patients undergoing stem cell transplant for hematologic malignancies showing a poorer prognosis in those with pretransplant iron overload and hyperferritinemia.[17] We are not aware of data showing the significance of hyperferritinemia in posttransplant patients with otherwise normal graft function. The 2 remaining patients in this category clearly demonstrated the strong likelihood of an underlying inflammatory process (fever, weight loss, pleural effusions) but, unfortunately, remained undiagnosed.

There are weaknesses in an analysis of this kind. Most prominently, it can be difficult to assign a single diagnosis to a multifactorial outcome. A markedly elevated serum ferritin level can arise from a wide variety of overlapping conditions, and it may be difficult to assign a primary cause in a patient with, for instance, both acute hepatic and chronic renal failure. We attempted to minimize the somewhat arbitrary nature of this assignment by using a simple algorithm, with disease states most associated with hyperferritinemia at the top and those where this association is less profound at the bottom. In this way, we feel we maximized our chances of correctly assigning the most likely etiology causing the highest burden of hyperferritinemia, even in patients with several conditions.

An additional difficulty arises from the nature of retrospective review of patient cases and the limitations of the data available. Up to a quarter of patients with apparent sepsis, for example, do not have documented infection.[18] It is possible that there are cases of autoimmune inflammatory disease in our cohort who were incorrectly diagnosed as "culture-negative" sepsis. These patients would not, in general, come to the attention of a rheumatologist, and it is possible that alternative diagnoses may not have been entertained.

Having a higher ferritin cutoff value is typically considered more valuable in predicting the presence of an underlying inflammatory disease. We used a cutoff value greater than 1000 μg/L. We did this because these values are more commonly encountered in the clinical setting, making our analysis more broadly applicable. Although patients in our study with inflammatory conditions such as AOSD or MAS/HLH did have significantly higher serum ferritin levels than those without, the majority of patients with serum ferritin levels greater than 10,000 μg/L carried diagnoses similar to the cohort as a whole.

Finally, our patient population is taken from a tertiary academic medical center and may not reflect a range of diseases or conditions that would more typically be encountered in general practice. In particular, our patients include a significant number of transplant patients, both solid and hematologic. It is possible that the causes of marked hyperferritinemia in a nonacademic medical center would trend more toward malignant and infection causes.

In conclusion, although a markedly elevated serum ferritin level may occur in the presence of an inflammatory disease, it is far more likely to accompany nonrheumatologic conditions such as malignancy, infection, or liver disease. In addition, there are patients with indolent levels of chronic inflammation who may appear well yet have extremely high ferritin levels.

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