

CLINICAL VIGNETTE

Elevated Ferritin Values and their Implications for Patient Care

John Barstis, M.D.

Case Report

A 60-year-old woman was diagnosed in 2011 with acute myelocytic leukemia. She was admitted to the leukemia service at UCLA and treated with seven days of induction chemotherapy Daunamycin and ARA-C, which resulted in the required complete aplasia of her bone marrow. She had a somewhat difficult, though not unusual hospitalization, which lasted for 92 days. During that time, she required units of packed red blood cells and units of single donor platelets. She achieved a complete marrow response. Because of her favorable cytogenetics, she was given four cycles of consolidation chemotherapy with high dose ARA-C and has been observed since that time without relapse. Given the high number of transfusions required during the course of her therapy, a ferritin of 2532 was obtained in December 2012. This was confirmed with a repeat value of 2457. No documentation of any previous iron studies was available. She was given the diagnosis of transfusion related iron overload and started therapeutic phlebotomies. After seven phlebotomies, her ferritin in December 2013 was 901; she was advised that a less intensive regimen would be adequate. However after a six month hiatus, her ferritin increased to 1227. This was unexpected, so HFE mutations were ordered to assess for an independent cause. She was found to be heterozygous for an H63D mutation. Therapeutic phlebotomies were resumed. Her ferritin values were erratic and did not show the expected sequential fall. Subsequent values have included 978, 1000, 1322, and 957. FE/TIBC have shown saturations of 10-15%, and frequency of

phlebotomies has been limited by Hgb of approximately 10.0–10.5. She had fourteen phlebotomies from March 2013 to November 2014.

Discussion

This patient presents with a complex process in which three different factors are contributing to her persistent high ferritin. She clearly had many transfusions during her treatment for AML. She is a heterozygote for the minor HFE mutation H63D, which although not associated with tissue damaging levels of iron storage, especially in women, does generally cause some excess iron retention and elevated ferritin levels. However, the fact that her ferritin remains at about 1000 after fourteen phlebotomies, and with plasma iron at deficiency levels, suggests her ferritin is acting as an acute phase reactant, for unknown reasons. It is possible that her therapy or her previous AML itself are causative factors, though it has been more than two years since any chemotherapy. She is likely cured after being disease free for more than three years. All studies to find other causes of inflammation have been negative, and she feels entirely well.

Management of iron by living organisms is a complex process, as it is both vital, and when present as free iron, toxic. Ferritin is a protein that stores iron in a nontoxic fashion, controls its release, and transports it to required areas of the body. Its serum value has been shown to correlate very well with total body iron stores. The clinical utility of a ferritin assay is very high, both for high and low values.

In general, it has been found that there are very few false positive low ferritin results, and a ferritin of less than ten is a reliable indicator of iron deficiency anemia. It is more reliable than a low serum iron concentration, which can fluctuate significantly, even on a day-to-day basis, due to many factors.

This is not true of a high ferritin. There are many reasons for a falsely high value as it can act as an acute phase reactant and not represent the true level of tissue iron stores. Most housestaff are familiar with such values as the values are often very high in critically ill patients. An extreme example is Hemophagocytic Lymphohistiocytosis (HLH) in which a ferritin of greater than 500 is a diagnostic criteria, with values of up to 40,000 often encountered.¹

Iatrogenic iron overload is most often seen in children with thalassemia major and in adults with Myelodysplastic Syndromes or Aplastic Anemia. In these patients, therapeutic phlebotomy is not an option; therefore, iron chelating agents must be used. The patient's course was unusual as such patients usually respond quickly to relatively few phlebotomies. The finding of a genetic component explained the slow response, although not the erratic values. The optimal level of iron reduction is unknown for both HFE heterozygotes and for iatrogenic iron overload.² Different faculty members suggested different ferritin goals: 300, 500, and simply less than 1000, though all agreed tissue damage is unlikely when ferritin is less than 1000.

The genetics of hemochromatosis are complex. Classical hemochromatosis is caused by homozygosity of the 282Y mutation. But patients homozygous for the H63D mutation also have clinically harmful iron overload and its associated consequences. It is generally accepted that patients homozygous for 282Y mutations should have their ferritin kept below 50, and possibly for H63D as well.³ Heterozygous patients are much less affected, but there is evidence that they also may have

increased rates of liver disease and neurodegenerative brain diseases due to variable recessive penetrance. Patients with any combination of heterozygous mutations have not been clearly shown to benefit from a precise ferritin target, and their clinical heterogeneity may be the reason.

In summary, the ferritin test is a valuable tool for patient care and is relevant in a broad range of different clinical settings. The fact that multiple causes can affect test result in the same patient requires vigilance and an understanding of all these factors.

REFERENCES

1. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007 Feb;48(2):124-31. PubMed PMID: 16937360.
2. Aguilar-Martinez P, Grandchamp B, Cunat S, Cadet E, Blanc F, Nourrit M, Lassoued K, Schved JF, Rochette J. Iron overload in HFE C282Y heterozygotes at first genetic testing: a strategy for identifying rare HFE variants. *Haematologica*. 2011 Apr;96(4):507-14. doi: 10.3324/haematol.2010.029751. Epub 2011 Jan 12. PubMed PMID: 21228038; PubMed Central PMCID: PMC3069226.
3. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS, American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011 Jul;54(1):328-43. doi: 10.1002/hep.24330. PubMed PMID: 21452290; PubMed Central PMCID: PMC3149125.