

### Question 23 – February 8

A 46 year old man with inflammatory arthritis is referred for an elevated ferritin. The patient reports pain in multiple joints for which he takes indomethacin. He also consumes 2 alcoholic beverages daily. There is no family history of liver disease. On physical examination, the patient's body mass index is 32. The liver span is 7.0cm and slightly firm. He is anicteric with no stigmata of chronic liver disease and the spleen is not palpable. Serum laboratory tests are as follows: ALT 52 U/L, AST 41 U/L, Alkaline phosphatase 76 U/L, bilirubin 0.9 mg/dL, INR 0.9, platelet count  $211 \times 10^3$  cells/ $\mu$ L, ferritin 1556  $\mu$ g/mL, iron 253  $\mu$ g/mL, transferrin saturation 88%.

What is the most appropriate next step?

- A. Begin therapeutic phlebotomy
- B. Perform a liver biopsy
- C. Recommend weight loss and recheck labs in 6 months
- D. Recommend a low iron diet and recheck labs in 6 months
- E. Begin iron chelation therapy

Answer: B

This patient likely has hereditary hemochromatosis. He has several potential causes of an elevated ferritin level, including inflammatory arthritis, obesity, and alcohol use. However, the concurrent elevations of transferrin saturation and aminotransferases in addition to the magnitude of the ferritin elevation make hereditary hemochromatosis the most likely cause. Hereditary hemochromatosis is an autosomal recessive disorder associated with increased iron absorption, resulting in iron deposits that may lead to arthritis, diabetes, endocrinopathy, heart disease, cirrhosis, and hepatocellular carcinoma. The most common form of hereditary hemochromatosis is caused by homozygous *C282Y* mutations of the *HFE* gene. A ferritin level higher than 1000 $\mu$ g/L is associated with a high prevalence (20%-45%) of advanced fibrosis and cirrhosis in hereditary hemochromatosis. Thus, liver biopsy is recommended to stage the degree of liver disease in *C282Y* homozygotes or compound heterozygotes if liver enzymes are elevated or if the ferritin level is above 1000  $\mu$ g/L. Therapeutic phlebotomy can slow disease progression in hereditary hemochromatosis, but would not be the appropriate next step before liver biopsy to evaluate for underlying fibrosis or cirrhosis. Obesity may raise ferritin levels as an acute phase reactant, but the concurrent elevations of transferrin saturation and aminotransferases make this a less likely primary contributing factor. Dietary modifications are not advised because iron depletion cannot be achieved with dietary changes alone. Although iron chelators are often administered to patients with secondary iron overload, such as those with hematologic disorders who may not tolerate phlebotomy, they are associated with more adverse effects and are much less effective for iron removal than phlebotomy.

Reference:

VanWagner, L. B. and R. M. Green (2014). "Elevated serum ferritin." *Jama* 312(7): 743-744.