Q2 Hemochromatosis

Which *one* of the following statements about hemochromatosis is *false*?

- ❍ 1. The earliest laboratory manifestation is an elevation in the serum ferritin level.
- ❍ 2. Iron elevation is a risk factor for breast cancer.
- ❍ 3. Arthritis may occur even after successful therapeutic phlebotomy.
- ❍ 4. Cardiomyopathy is a rare complication that is potentially reversible with iron-removal therapy.

Educational Point: Hemochromatosis comprises a group of inherited disorders that can cause iron overload, which primarily affects the liver and joints and results from a failure in the regulation of the key liver-derived iron regulatory hormone hepcidin to respond to increasing iron stores.

Hemochromatosis may be characterized by elevations in serum transferrin saturation, ferritin levels, or hematologic measures. Since iron-related laboratory measurements vary, a sustained elevation must be documented on multiple occasions. **The earliest manifestations of hemochromatosis are elevations in serum transferrin saturation, mean red-cell hemoglobin level, and red-cell volume. These changes precede an elevation in the serum ferritin level.**

General population screening for hemochromatosis has not been recommended because of variable and incomplete penetrance and lack of any proof of a resulting survival advantage.

Symptoms are nonspecific and often equally prevalent among persons with and those without hemochromatosis. The most common symptom, fatigue, is observed primarily in men with serum ferritin levels that are higher than 1000 µg/L.

The most frequent clinical manifestations are liver disease (advanced liver fibrosis or cirrhosis and primary liver cancer) and arthritis. Oxidative stress-related tissue injury is responsible for the pathogenesis of the disease. Among men but not women, the risk of liver disease is significantly increased, by a factor of 4.3, for p.C282Y homozygotes as compared with men who do not have *HFE* variants; the risks of arthritis and colorectal cancer are doubled, and the risks of pneumonia and diabetes mellitus are increased by a factor of 1.5. Among women who are homozygous for p.C282Y, the risks of colorectal cancer and breast cancer are doubled and the risk of arthritis is increased by a factor of 1.3, as compared with women who do not have *HFE* variants. **Although it is not clear whether the predispositions to colorectal and breast cancers are *HFE*- or iron-related, epidemiologic observations indicate that iron elevation is a risk factor for breast cancer.**

Serum iron levels at the upper end of the reference range, but in the absence of iron overload, have been reported to be a risk factor for primary liver cancer, supporting a direct role of iron in carcinogenesis. Furthermore, therapeutic phlebotomy significantly reduces the risk of cancer, adding further credibility to the role of iron in the development of cancer.

However, type 2 polyarticular osteoarthritis, characterized by arthropathy of the second to fifth metacarpophalangeal joints or bilateral large-joint arthropathy (involving radiocarpal, elbow, hip, knee, or ankle joints), is 8 times as common in patients with hemochromatosis as in those without the disorder. It is unclear why arthropathy affects only a subgroup of people with hemochromatosis. **Arthritis may occur at any point during the natural history of hemochromatosis, even after successful therapeutic phlebotomy.** Risk factors for arthritis include increased age, advanced liver fibrosis, serum ferritin levels exceeding 1000 µg/L, and serum transferrin saturation above 50% for at least 6 years.

A variety of other conditions occur with hemochromatosis, including hyperpigmentation, diabetes mellitus, hypogonadotropic hypogonadism, and cardiomyopathy. These conditions are usually managed according to the standard of care and in addition to the usual treatment of iron overload. **Cardiomyopathy is one of the rare complications that is potentially reversible with iron-removal therapy.**