Iron-overload myopathy

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A 66-year-old male patient presented with a 4-month history of progressive muscle weakness. Twelve years prior to presentation he was evaluated for fatigue, weight loss, new-onset diabetes and elevated liver enzymes and was diagnosed with hereditary hemochromatosis, homozygous for the C282Y mutation in the HFE gene. His total iron at diagnosis was 137 mcg/dL; iron binding capacity, 149 mcg/dL; serum ferritin, 3200 ng/mL; and quantitative iron, 24184 mcg/g dry weight of liver. This resulted in a hepatic iron index of 7.9. He was treated with monthly phlebotomies once the diagnosis of hemochromatosis was made. He had received a liver transplant 10 years prior to presentation for hemochromatosis-induced liver failure. He developed post-transplant renal failure due to calcineurin inhibitors, and was started on hemodialysis 20 months prior to presentation. Nine months prior to presentation he was evaluated due to mildly elevated liver function tests; a liver biopsy showed marked cholestasis, increased parenchymal iron (Fig. 1a, regular histochemistry and Fig. 1b, Prussian blue stain), but no signs of acute cellular rejection. At the time of presentation, his medications included tacrolimus, ursodeoxycholic acid, mycophenolate mofetil and levothyroxine; however, he had not been taking steroids for the last 9 years. Physical exam revealed diffuse muscle atrophy and severe proximal myopathy that impaired his gait. Laboratory tests revealed elevated serum ferritin (2985 ng/mL). Creatinine phosphokinase, aldolase, potassium, calcium,

thyroid and liver function tests were within normal limits. Electromyography showed a generalized myopathic process with increased membrane irritability and a superimposed peripheral neuropathy. Muscle biopsy taken from the right quadriceps showed severe hemosiderosis, which was predominantly subsarcolemmal, and moderate type-2 fiber atrophy, without signs of inflammation. Prussian blue stain demonstrated prominent iron deposits in the muscle (Fig. 1c, low power and Fig. 1d, high power). Phlebotomy was offered as a treatment option; however, the patient opted for hospice care.

Hereditary hemochromatosis is an autosomal recessive disease characterized by iron overload due to increased intestinal iron uptake. As in our case, most patients with hereditary hemochromatosis have the C282Y mutation in the HFE gene. Several organs are affected by chronic iron deposition, mainly the liver, endocrine glands, and heart. Patients on hemodialysis are at particular risk for developing hemosiderosis [1]. HLA-A3, B7, and B14 antigens are associated with idiopathic hemochromatosis and were tested in hemodialysis patients, some of them with myopathy, showing correlation between presence of the HLA-antigens and serum ferritin levels [2]. Patients on maintenance hemodialysis carrying these hemochromatosis-related antigens have an increased risk of iron overload and muscle iron deposition [2]. It remains unclear, however, why iron deposition in skeletal muscle is not more frequent in patients with hemochromatosis. Does hemodialysis start or accelerate iron deposition in muscles of patients with hemochromatosis? To our knowledge this is the first documented case of a clinically devastating iron-overload myopathy in a patient with hereditary hemochromatosis. Excess iron is toxic to the tissues mainly by causing lipid peroxidation via iron-catalyzed free radical reactions, stimulation of collagen formation and interaction of

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Fig. 1 **a** Liver biopsy, regular histochemistry. **b** Liver biopsy, Prussian blue stain. **c** Muscle biopsy, Prussian blue stain, low power. **d** Muscle biopsy, Prussian blue stain, high power

reactive oxygen species and of iron itself with DNA, leading to lethal cell injury. These mechanisms have been studied in the liver. Little is known regarding the toxic mechanisms in skeletal muscle.

Conflict of interest The authors report no conflicts of interest.

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