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Case Report

Hemochromatosis in Two Female Olive Baboons (*Papio anubis)*

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This report describes hemochromatosis associated with chronic parenteral iron dextran administration in 2 female olive baboons (*Papio anubis)*. These baboons were enrolled on an experimental protocol that induced and maintained anemia by periodic phlebotomy for use in studying potential treatments for sickle cell anemia. The 2 baboons both presented with clinical signs consistent with iron overload, including decreased appetite, weight loss, elevated liver enzymes, and hepatosplenomegaly. Histopathologic findings supported a morphologic diagnosis of systemic hemosiderosis, as evidenced by the overwhelming presence of iron in the reticuloendothelial system and liver after the application of Prussian blue stain. This finding, combined with the clinical presentation, lead to a final diagnosis of hemochromatosis. This case report suggests that providing anemic patients with chronic parenteral iron supplementation in the absence of iron deficiency can result in iatrogenic iron overload and subsequent systemic toxicity. Furthermore, these subjects may present with hemochromatosis and its associated clinical signs many years after cessation of iron supplementation.

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Iron is an essential micronutrient that plays an important role in cellular proliferation, oxygen transport, and cellular energy generation.[13,26,31] The highest levels of iron in the body is found in the erythrocytes, followed by the liver, reticuloendothelial system, and skeletal muscle.[9] Three main mechanisms regulate iron: 1) dietary absorption through the proximal duodenum; 2) recycling of senescent red blood cells by macrophages; and 3) storage in the liver. The liver produces the hormone hepcidin, which is the primary negative regulator of systemic iron metabolism.[38] Hepcidin controls the release of iron from enterocytes and macrophages into the circulation by binding to and degrading ferroportin, the only mammalian iron exporter.[35] When plasma iron levels are high, hepatocytes increase hepcidin synthesis. The increased hepcidin subsequently suppresses gastrointestinal absorption of exogenous iron and iron release from macrophages into circulation.[31]

Approximately 1 to 2 mg of iron is lost per day through enterocyte and skin sloughing.[38] Iron can also be lost by hemorrhage, menstruation, and parasitic infestation.[38] Other than these, the body has no active mechanism for iron excretion. Iron overload can result from acute iron toxicity or chronic accumulation of iron over time.[35] Iron is primarily stored in the liver in the form of ferritin, and excess iron is transformed into hemosiderin, an oxidized form of ferritin. Hemosiderin is an iron-containing pigment found primarily in macrophages and hepatocytes.[35]

Hemosiderosis occurs when iron accumulates in tissues, but causes no subsequent organ injury or dysfunction. It is not typically pathologic and can be reversed.[9] In contrast, hemochromatosis occurs when iron accumulation results in organ injury and dysfunction.[35] The 2 types of hemochromatosis are primary and secondary. Primary hemochromatosis, also known as hereditary hemochromatosis, is the result of inherited mutations in genes that are important for iron homeostasis. The most common gene involved in primary hemochromatosis is *HFE*, an autosomal recessive trait.[11] Almost all forms of primary hemochromatosis involve low levels of hepcidin expression.[11] Secondary hemochromatosis can occur due to iron-loading anemias such as thalassemia and sideroblastic anemia, chronic liver disease (for example, hepatitis C), and iatrogenic causes, such as excess iron in the diet or parenteral administration.[16] Hemolytic anemia and repeated blood transfusions can also result in secondary hemochromatosis.[35] In primary hemochromatosis, iron typically accumulates in the liver, pancreas, heart, and endocrine glands for many years.[16,24] In contrast, secondary hemochromatosis patients often accumulate iron in the reticuloendothelial system, bone marrow, and lymph nodes[16] over a shorter time period,[24] with excess iron accumulating in the hepatocytes after the reticuloendothelial system has become saturated with iron.[16] Symptoms of iron overload can vary among individuals due to the number of organ systems affected. These symptoms may include lethargy, arthralgia, skin hyperpigmentation, abdominal pain, abnormal liver chemistry tests, and hepatomegaly.[15] In the current report, we describe 2 cases of hemochromatosis in female baboons after chronic parenteral administration of iron dextran as part of an anemia maintenance protocol used to study sickle cell anemia treatments.

Case Study

Two juvenile intact female olive baboons (*Papio anubis)* were acquired from a national primate research center. Baboon 1 and Baboon 2 were approximately 2.1 y old and weighed 6.0 kg and 5.5 kg respectively upon arrival. The animals were born to different dams housed in separate breeding corrals. Paternity

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testing was not performed, but they were unlikely to have the same sire. The animals were healthy and tuberculosis-free as determined by physical examination, complete blood count, serum chemistry analysis, fecal evaluation, and intradermal tuberculin skin testing. The baboons originated from a colony known to be positive for simian T-cell leukemia virus (STLV) and *Papiine herpesvirus 2* (HVP2), but confirmatory testing for these viruses was not performed in these 2 baboons.

The baboons were socially housed in accordance with the *Guide for the Care and Use of Laboratory Animals*,[17] Public Health Service Policy,[30] and the Animal Welfare Act and Regulations[3,4] at the University of Illinois at Chicago, a fully AAALAC-accredited institution. All procedures involving animal care and use were approved by the IACUC at the University of Illinois at Chicago. The baboons received 15% Monkey Diet (number 8714, Envigo-Teklad, Madison, WI) once daily and received municipal tap water without restriction. The diet was supplemented with fresh produce or foraging mix once daily. Manipulable enrichment items were placed directly in cages and rotated every 2 wk.

In patients with sickle cell disease, high fetal hemoglobin levels can reduce the severity of symptoms and increase their life span.[2] The 2 baboons were assigned to an experimental protocol to assess how sickle cell disease therapies affect fetal hemoglobin levels. To evaluate sickle cell disease therapies during erythropoietic stimulation, which is the situation during sickle cell disease, anemia was induced in the baboons. While on the experimental protocol, these animals received various sickle cell disease therapies intermittently over a period of 8 to 10 y.

Anemia was induced by repeated phlebotomy every 3 to 4 d to attain a hematocrit of 20% within 10 d. This was typically achieved by removing 15% of total blood volume (based on 7% of body weight in kilograms) during each phlebotomy session. Animals were maintained at the target hematocrit by periodic phlebotomy as needed over approximately 10 to 60 d. An equivalent volume of Lactated Ringers Solution (Baxter, Deerfield, IL) was given as replacement fluid. Depending on the experimental manipulation, animals received the following intramuscular supplements: iron dextran (100 mg/mL; Henry Schein Animal Health, Dublin, OH); folic acid (5 mg/mL; Ben Venue Laboratories, Bedford, OH); vitamin B_{12} (1000 mcg/mL; Somerset Therapeutics LLC, Mendham, NJ); and vitamin B complex (150 mg/mL; Henry Schein Animal Health, Dublin, OH). Folic acid and B vitamins were provided to facilitate the production of erythrocytes.[10] When phlebotomized, baboons also received intramuscular iron dextran and folic acid (0.3 mg) to maintain sufficient iron stores to allow a robust reticulocyte response. The amount of iron dextran needed for replacement was based on the following equation: replacement iron (mg) = blood loss (mL) x hematocrit (%).[19] For example, if 100 mL of blood was removed with a hematocrit of 35%, approximately 35 mg of iron was supplemented via intramuscular injection. Vitamin B_{12} (0.2 to 0.4 mg) was given every other blood draw, while vitamin B complex (30 to 60 mg) was given every third blood draw. Based on the laboratory's anemia management protocol, on average an animal would receive approximately 375 mg of iron dextran, 5 mg of folic acid, 1 mg of vitamin B_{12}, and 115 mg of vitamin B complex per experiment. The baboons also received intermittent bone marrow aspirations to assess effects of experimental drug treatments on DNA methylation, histone modifications, and gene expression.

Baboon 1 was used in 11 experiments, phlebotomized 182 times, and received approximately 4.5 g of parenteral iron over an 8-y period. Baboon 2 was used in 13 experiments, phlebotomized 114 times, and received approximately 4.2 g of parenteral iron over a 10-y period. Complete blood counts were performed during phlebotomy to assess hematocrit and anemia. Neither baboon showed microcytic hypochromic anemia during experimentation, although this is a common finding in patients with an iron deficiency anemia. Anemias in these animals were consistently classified as mild to moderate macrocytic hypochromic regenerative anemia. Overall, 24 baboons, over a period of 14 y, have participated in this experimental protocol. Only the 2 animals presented in this case report developed clinical signs related to iron overload.

Clinical Presentations. ***Baboon 1.*** Baboon 1 (9.2 y old) presented with clinical signs of iron overload while being used for a study to evaluate bone marrow ex vivo. This baboon had not received sickle cell disease therapies for over 25 mo. She demonstrated anorexia, weight loss (23% weight loss from baseline), and loss of body condition (body condition score of 2 on a 9-point scale). Physical exam revealed mild gas distension of the intestines and pale mucous membranes, and a complete blood count demonstrated a moderate macrocytic hypochromic regenerative anemia. Serum chemistry panel showed a moderate to severe increase in the hepatic enzymes alkaline phosphatase (ALP) and aspartate aminotransferase (AST), as well as a moderate increase in total bilirubin. Figure 1 provides complete blood count and serum chemistry values. Abdominal radiographs revealed a markedly enlarged liver and possible splenomegaly. The decision for humane euthanasia was multifactorial, but included a percentage weight loss that met study endpoint criteria, hepatosplenomegaly, and historical exposure to STLV. Based on the animal's history and clinical presentation, a presumptive diagnosis of lymphoma due to STLV infection was made. Upon necropsy, the liver and spleen were found to be markedly enlarged, with normal color (Figure 2 A). Thoracic and peripancreatic lymph nodes were also enlarged (Figure 2 B). Histopathology of the liver showed histiocytic macrophages and hepatocytes were filled with brown granular pigment, suggestive of hemosiderin. Clusters of hepatocytes were vacuolated with ill-defined cytoplasmic clear spaces. Prussian blue stain was applied to a section of liver, confirming the brown pigment as iron positive. The red pulp of the spleen was expanded with erythrocytes and hematopoietic cells of erythroid lineage. Hemosiderin laden macrophages were observed in renal glomeruli and in the interstitial capillaries of the kidney, lung, myocardium, colon, jejunum, pancreas, and adrenal glands. Bone marrow histology revealed marked erythroid hyperplasia and iron accumulation. No other gross lesions or abnormalities were seen. The morphologic diagnosis included lymphadenomegaly, hepatosplenomegaly, and systemic hemosiderosis due to iron overload. The final clinical diagnosis of hemochromatosis was made based on the morphologic diagnosis of systemic hemosiderosis, combined with the animal's clinical presentation and history of chronic parenteral iron administration. We did not test for STLV because the overwhelming evidence supported hemochromatosis as the primary cause for the animal's clinical presentation.

Baboon 2. Baboon 2 (13 y old) presented with inappetence while on a study to evaluate bone marrow ex vivo. This baboon had not received sickle cell disease therapies for over 70 mo. Physical exam revealed marked organomegaly in the cranial abdomen. Complete blood count revealed a mild macrocytic hypochromic regenerative anemia. Serum chemistry panel showed a moderately increased ALP. Figure 1 shows complete blood count and serum chemistry values. Abdominal radiographs revealed hepatosplenomegaly. Exploratory abdominal surgery was performed the day after the initial clinical presentation.

Select hematologic values	Baboon 1	Baboon 2	Reference ranges
RBC (x10³/uL)	2.18	3.45	4.86 ± 0.59
Hgb (g/dL)	5.2	9.0	12.3 ± 1.7
Hct (%)	19.4	29.9	37.4 ± 5.0
MCV (fL)	89	87	77.7 ± 6.3
MCHC (g/dL)	26.9	26.2	32.8 ± 1.1
Select clinical chemistry values			
ALP (U/L)	2453	1225	254 ± 306
ALT (U/L)	55	14	44 ± 40
AST (U/L)	74	15	34 ± 16
Alb (g/dL)	2.23	2.08	3.2 ± 1.4
tBili (mg/dL)	0.56	0.21	0.2 ± 0.1

Figure 1. Select hematologic and clinical chemistry values from Baboon 1 and Baboon 2 at the time of clinical presentation. Text in red highlights abnormal values. Normative hematologic and clinical chemistry reference ranges are also provided for female *Papio* spp. adapted from Fortman and colleagues[10] Values are presented as mean ± SD. RBC: red blood cells; Hgb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate aminotransferase; Alb: albumin; tBili: total bilirubin.

During surgery, marked hepatosplenomegaly was confirmed. Miliary white foci were present throughout all liver lobes. We elected to perform humane euthanasia due to a presumptive diagnosis of lymphoma caused by STLV infection. The histopathology results were similar to those seen in Baboon 1. Briefly, Prussian blue stain was applied to a section of liver and confirmed that histiocytic macrophages and hepatocytes contained iron (Figure 3 A through C). The red pulp of the spleen revealed foci of extramedullary hematopoiesis with red cell and myeloid precursors. Marked accumulation of hemosiderin was also noted in macrophages of the spleen, kidney, lung, small intestine, stomach, and lymph nodes, and confirmed as iron with Prussian blue staining (Figure 4 A through C). Bone marrow histopathology was not performed. No other gross lesions or abnormalities were seen. The morphologic diagnosis was systemic hemosiderosis. The final clinical diagnosis was hemochromatosis due to excess iron administration. STLV testing was not performed.

Discussion

Iron homeostasis is a vital process that can prevent iron overload and iron deficiency by regulating levels in plasma and tissues for normal function. Systemic hemosiderosis is the result of excess iron accumulation in tissues.[9] Excessive iron accumulation in tissues can cause cell death and organ dysfunction due to free radical formation and lipid peroxidation,[23] a condition known as hemochromatosis.[35] Conversely, iron deficiency can result from inadequate intake of iron in the diet, excess loss of iron during acute or chronic blood loss[25] or inadequate absorption of iron caused by gastrointestinal dysfunction such as short-bowel syndrome, inflammatory bowel disease, and protein-calorie malnutrition.[18] Iron supplementation can be used to restore iron homeostasis in anemic subjects, with the amount administered based on the degree of anemia, underlying pathology, red blood cell count, serum iron panel, and erythrocyte morphology.[25] Iron dextran administration is considered as a standard treatment for iron deficiency anemia in veterinary medicine.[21] Parenteral iron administration has also been used to treat anemia of chronic disease[34] and prophylactically in neonatal animals.[7]

The baboons described in this case report underwent an anemia maintenance protocol that involved chronically repeated phlebotomies. Parenteral iron dextran was administered prophylactically to maintain iron homeostasis in these animals. While neither animal presented in this case report exhibited clinicopathologic findings indicative of iron deficiency anemia (such as a microcytic, hypochromic anemia), parenteral iron supplementation was thought necessary to maintain iron homeostasis due to the iron lost during blood removal for anemia induction and maintenance. However, the hematologic findings suggest that these animals were never in need of iron supplementation and consequently developed systemic storage of excess iron. As part of the experimental protocol, the baboons in this case report received various sickle cell disease therapies, most commonly decitabine. Decitabine is an antineoplastic agent approved for the treatment of myelodysplastic syndromes in humans.[27] At high doses, this drug has been reported to cause increases in liver clinical pathology values (ALT, bilirubin), but only in patients with underlying liver disease.[27] The baboons also received another antineoplastic agent, hydroxyurea, during the study. Hydroxyurea has been known to cause elevations in AST and bilirubin in humans, which are generally self-limiting and resolve rapidly.[28] However, rare cases of acute mild hepatitis and severe lethal hepatitis-like injuries have occurred in patients taking hydroxyurea.[28] In these cases, lethal hepatitis occurred several months after discontinuation of hydroxyurea, although the patient was taking other hepatotoxic agents at the time of death.[28] The use of these antineoplastic agents may have compromised liver function in the baboons presented in this case report. We theorize that the use of the antineoplastic agents, combined with excess iron administration, predisposed these animals to develop clinical signs related to iron overload.

The baboons in this study received supplementation with folic acid, vitamin B_{12}, and vitamin B complex. Vitamin B_{12} and folic acid are necessary for the normal production of red blood cells and the avoidance of megaloblastic anemia.[10] Similarly, supplementation with vitamin B complex (vitamins B_1 through B_8, except B_3 and B_7) can enhance iron metabolism and mobilization.[10] Parenteral iron dextran, folic acid, and B vitamins were administered prophylactically in multiple experiments over

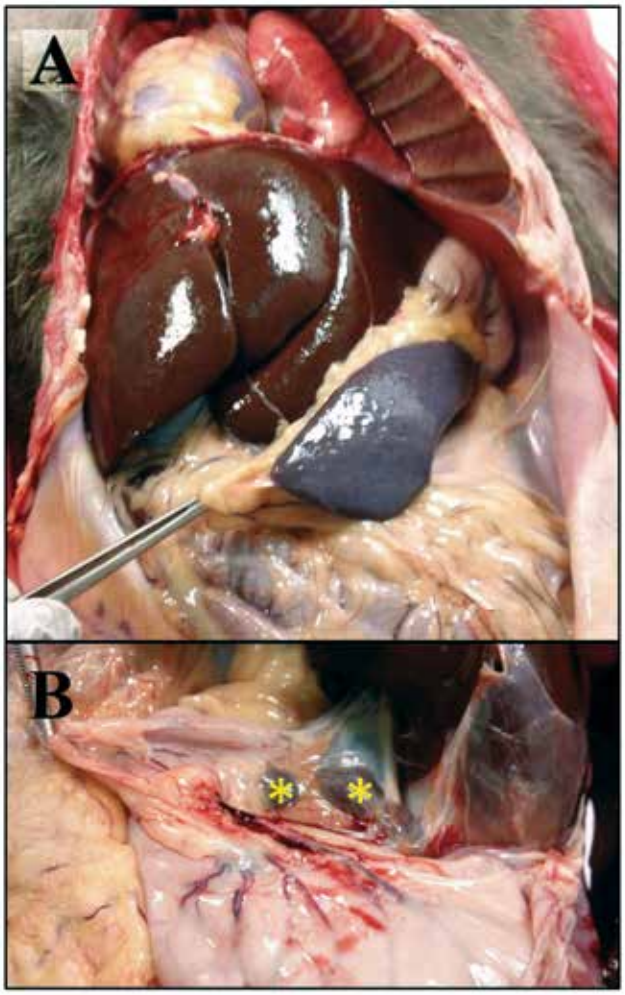

Figure 2. Representative gross necropsy images from Baboon 1 with hepatomegaly, splenomegaly (A) and lymphadenomegaly of the peripancreatic lymph nodes (B) due to iron accumulation caused by chronic parenteral administration of iron dextran. Yellow asterisks indicate the peripancreatic lymph nodes.

many years. The addition of these supplements probably contributed to increasing the uptake of systemic iron.

Hematologic parameters such as total serum iron, total iron-binding capacity, transferrin, ferritin, erythropoietin, and hepcidin were not measured as part of the experimental protocol. Iron quantification assays are inherently variable as iron status can be altered by many confounding factors, such as inflammation, hepatocyte dysfunction, increased cell death, and oxidative stress.[24] Studies evaluating iron assays in lemurs[36] and marmosets[33] acknowledge a lack of standardized methodologies for iron status evaluation in nonhuman primates. However, one study suggests that ferritin, serum iron concentration, and percent transferrin saturation may be useful to assess hemosiderosis antemortem in callitrichid species.[33] A study assessing the effects of weekly blood collection in cynomolgus macaques (*Macaca fascicularis*) measured serum iron levels by using a spectrophotometric assay. The results of this study were highly variable and proved to be an unreliable measure of systemic iron.[1] Moreover, the majority of baboons used on our anemia maintenance protocol showed no clinical evidence of iron overload; therefore, iron levels were never evaluated as part of the experimental protocol. In addition, standardized methodologies or published reference ranges are not available to aid in evaluating iron status in baboons antemortem. Biopsy of the liver can help to assess liver iron concentration in focal areas of liver.[37] Ultrasound and computed tomography cannot detect iron overload, and findings using these methodologies are nonspecific.[15] However, magnetic resonance imaging (MRI) is highly sensitive and can quantify diffuse iron deposition in the liver. Local magnetic field inhomogeneity caused by the paramagnetic effect of hemosiderin results in reduced signal intensity in the liver parenchyma.[6] These iron quantification procedures were not performed in our baboons.

One group induced hepatic iron overload in experimentally naïve baboons by administering iron intramuscularly 3 to 5 d a week, with total iron administration of 20 to 26 grams over a 15-mo period.[5] The baboons in that study demonstrated marked hepatic hemosiderosis up to 14 mo after the last administration. Most of the iron was located in the reticuloendothelial system, similar to the histopathologic findings of the 2 baboons presented in this case report. In the current case report, anemic baboons received roughly 4.2 to 4.6 grams of iron throughout an experimental period of 8 to 10 y; this is about 20% of the total iron used in the cited iron overload study. Our baboons received less parenteral iron over a longer time period, yet their histopathologic results were similar to the previous study.[5] Thus, both studies indicate that iron is stored in the body for extended periods of time, whether it is needed or not. This storage of excess iron may eventually lead to clinical abnormalities, despite an extended long period of time since the cessation of iron supplementation.

A total of 24 baboons have been used on our anemia maintenance protocol, yet only 2 developed clinical signs related to systemic iron accumulation. We also had the opportunity to assess iron accumulation in a third olive baboon, a 14-y-old female that had been previously assigned to the anemia maintenance protocol. This animal was euthanized for tissue collection for an unrelated study and was asymptomatic at the time of death. While on the anemia maintenance protocol, she was phlebotomized 75 times and received approximately 2.5 g of iron over a 5-y period. Her last iron injection and sickle cell disease therapy administration was 5 y prior to necropsy. A complete blood count and serum chemistry were performed prior to necropsy and revealed no abnormalities. Despite having received no parenteral iron or experimental drugs for several years, histopathology revealed a morphologic diagnosis of systemic hemosiderosis. Specifically, the liver showed marked expansion of portal triads with hemosiderin laden macrophages. Hepatocytes throughout the liver had mild vacuolar change and contained variable amounts of hemosiderin (Figure 3 D through F). The spleen contained numerous hemosiderin laden macrophages throughout the red pulp, with mild to moderate extramedullary hematopoiesis. Several lymph nodes also contained variable numbers of hemosiderin laden macrophages (Figure 4 D through F). The kidney demonstrated low numbers of hemosiderin laden macrophages in the blood vessels, glomeruli, and in the interstitium of the cortex and medulla. The bone marrow showed marked erythroid hyperplasia, with no evidence of iron accumulation. No other abnormalities were observed. These findings support the cumulative nature of iron storage after chronic parenteral administration. Although we have not fully investigated the remaining study population, we presume that other asymptomatic animals may have some degree of hemosiderosis, based on the histopathology findings in this animal.

Several factors could explain why this third baboon, and potentially others, were asymptomatic while Baboon 1 and Baboon 2 developed clinical signs. The first is that the third baboon

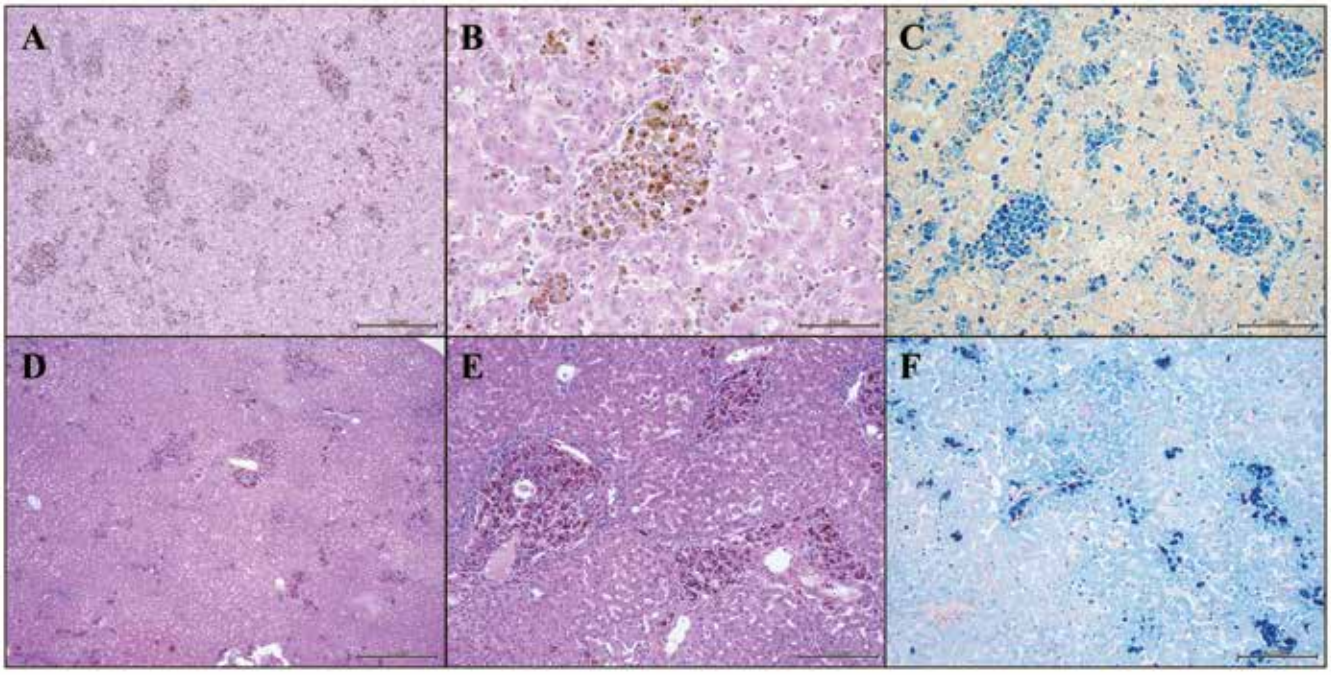

Figure 3. Representative histopathology of the liver from Baboon 2 (A through C) and from the asymptomatic baboon (D through F). There are numerous small aggregates of macrophages laden with brown granular pigment (hemosiderin) in portal stroma and in segments of hepatic sinusoids. Hepatocytes are stippled with brown, granular pigment. Prussian blue stain (C and F) confirms the brown pigment to be hemosiderin, an iron storage complex. Image A and D scale bar = 500 µm, image B = 100 µm, and images C, D, E, and F = 200 µm.

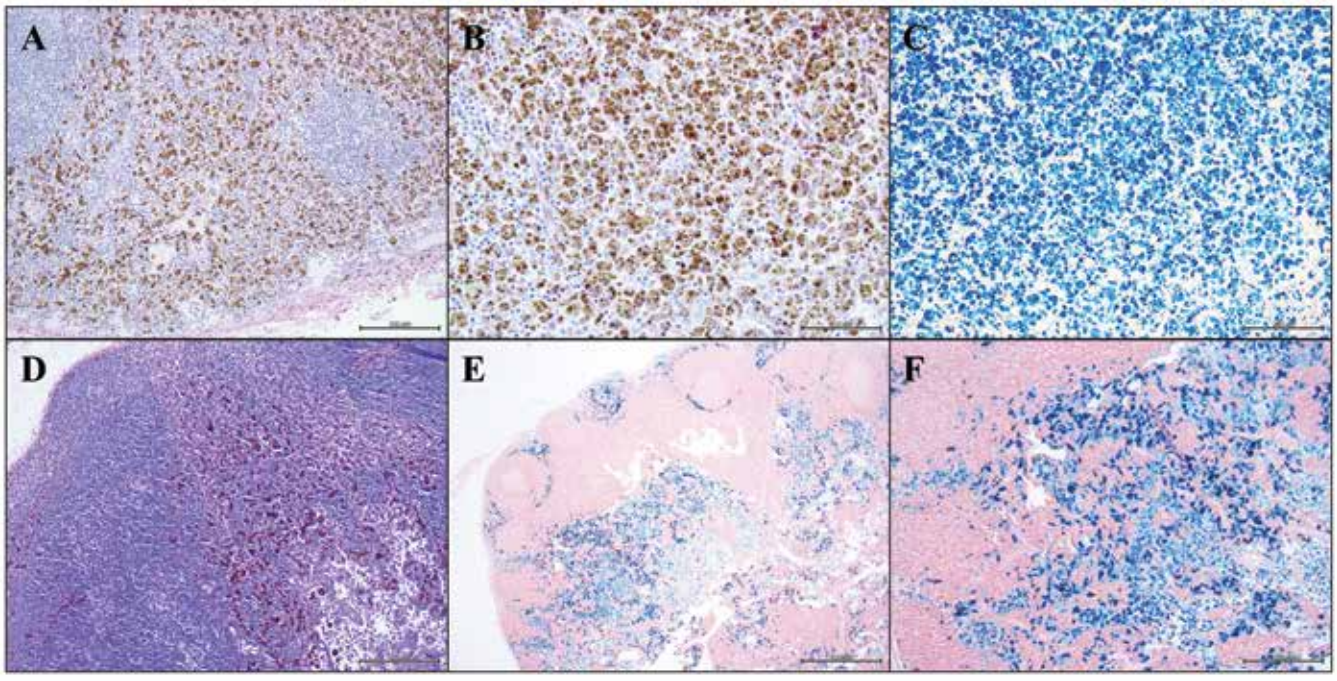

Figure 4. Representative histopathology of the lymph node from Baboon 2 (A through C) and from the asymptomatic baboon (D through F) shows macrophages laden with hemosiderin. Prussian blue stain (C, E and F) confirms the brown pigment to be hemosiderin, an iron storage complex. Image A, D and E scale bar = 500 µm, image B = 100 µm, and images C and F = 200 µm.

received approximately half the amount of parenteral iron dextran administered to the other 2 animals. Second, this baboon had been on study for only 5 y while Baboon 1 and 2 were on study for 8 to 10 y. The study duration not only correlates with the amount of parenteral iron given, but also with the amount of experimental drug therapies received. In addition, although iron quantification was not performed, histologic images of the liver and lymph node from the third baboon subjectively show a lesser degree of iron accumulation in these organs (Figures 2 to 3). Finally, the asymptomatic baboon had iron accumulation in fewer organs than the baboons that displayed clinical signs. For example, Baboon 1 had hemosiderin deposition in the liver, spleen, lymph nodes, heart, gastrointestinal tract, pancreas, adrenal glands, kidney, and bone marrow. Baboon 2 had

hemosiderin deposition in many of the same organs and tissues as Baboon 1, with the exception of heart, pancreas, and adrenal glands. Subjectively, the hepatocytes of Baboon 1 and Baboon 2 also had more severe vacuolar degeneration than the asymptomatic baboon. Therefore, the combination of iron administration, lengthy study duration, and exposure to potentially hepatotoxic experimental drugs resulted in systemic hemosiderosis. The presence of hepatocellular degeneration likely predisposed Baboon 1 and 2 to the development of clinical signs related to iron overload, and ultimately a diagnosis of hemochromatosis.

The recommended iron concentration in diets formulated for nonhuman primates is 100 mg/kg based on dry matter content.[29] The commercial diet fed in our nonhuman primate colony contains 320 mg/kg of iron. Based on this iron concentration, baboons in this case report were receiving 3.2 times more iron than required through their diet alone. We suspect that baboons on the anemia maintenance protocol were never iron deficient, because the diet provided sufficient iron to replenish systemic stores. Therefore, the administration of parenteral iron dextran was unnecessary and caused excess iron accumulation (systemic hemosiderosis) with subsequent clinical and hepatocellular abnormalities (hemochromatosis). Hepatic hemosiderosis is not commonly recognized in squirrel monkeys, macaques, or baboons,[8] but can be an incidental finding in marmosets,[22] lemurs,[8] and muriquis.[32] Some believe that this finding is due to excess iron in the diet.[8,20,22] While dietary iron overload is possible, the diet may be a more prudent option for supplementation, as oral iron is subject to intestinal regulatory mechanisms.[18]

Here we presented 2 cases of hemochromatosis in adult female baboons on an induced-anemia protocol. The combined findings of decreased appetite, weight loss, increased liver enzymes, and hepatosplenomegaly were likely a result of hepatocellular damage and liver dysfunction due to the combined toxic effects of iron accumulation and sickle cell disease therapies. The storage of iron in the liver and reticuloendothelial system seen in these animals likely occurred in response to excess iron saturation.[16] We propose a diagnosis of secondary hemochromatosis, induced iatrogenically by chronic administration of chronic parenteral iron dextran, despite lack of evidence for iron deficiency anemia. Although genetic testing was not performed to definitively exclude primary hemochromatosis, this is unlikely given the clinical history and pedigrees of these animals. In addition, nonhuman primates with primary hemochromatosis have not been reported to our knowledge. More research is needed to assess the prevalence of hereditary hemochromatosis in nonhuman primate species.

While supplemental iron is beneficial for treating iron deficiency, it is not recommended as a treatment for other forms of anemia, as iron overload can occur.[14] If iron supplementation is warranted in patients with healthy gastrointestinal tract absorption, we recommend initiating oral iron supplementation. The use of parenteral iron dextran carries an inherent risk, in that it bypasses the intestinal mechanisms for regulation of iron absorption.[18] Therefore, we caution against the use of injectable iron dextran in cases where iron deficiency has not been diagnosed due to the cumulative nature of this micronutrient and the subsequent potential for toxicity.

MRI is a sensitive and noninvasive approach for assessing liver iron concentrations.[6,15,16,37] If a patient requires chronic iron supplementation, frequent MRI is recommended to monitor changes in liver iron concentration over time. MRI was not used for the baboons described in this case report. For the remaining animals on the induced-anemia protocol, parenteral iron dextran was replaced with oral iron supplementation. Since the recommendation to switch to oral supplementation, we have not observed clinical signs of iron overload. We recommend complete evaluation of a patient's clinical presentation and history, along with diagnostic evidence of iron deficiency, such as a microcytic hypochromic anemia, prior to initiating chronic parenteral iron administration.

Chelation agents and frequent phlebotomies have been shown to reduce iron stores and improve survival in patients with secondary hemochromatosis.[24] However, the potential for hepatotoxicity in animals receiving chronic iron administration and their reduced utility for future studies is an important consideration. In the animals presented in this case report, the degree of iron overload was unknown at the time of clinical presentation and therefore, treatments targeted at iron reduction were not pursued. Given our new recommendation for this protocol, we do not expect additional animals to develop clinical signs of iron overload.

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