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Renal Transplantation and Evolution of Hemochromatosis: A Clinical Case Report

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DESPITE BEING one of the world's most frequent autosomal recessive diseases,[1–5] there are very few cases in the literature concerning hereditary hemochromatosis and renal transplantation.

CLINICAL CASE

A 66-year-old white woman received a cadaveric kidney allograft on 4 April 1999. Her past clinical history included lung tuberculosis in infancy, one episode of acute glomerulonephritis when she was 17, hypertension since she was 23, and preeclampsia on both her two term pregnancies. She began a regular hemodialysis program 7 years ago, when she was 59, due to end-stage renal disease, probably related to an ongoing chronic glomerulonephritis. No biopsy was performed.

While on dialysis, she had chronic anaemia compensated with recombinant human erythropoetin (rHuEPO) and occasionally intravenous iron. In addition, there was a fluctuating rise of hepatic transaminases, although the AgHBs and both anti-HCV antibody and HCV-PCR were all negative, and there was no history of ethanol abuse. Serum transferrin saturation and ferritin were also elevated in the last 2 years before transplantation, but she had no symptoms associated with parenchymal iron overload (see Table 1). In April 1998 she was diagnosed with a reactivation of lung tuberculosis, with Koch bacilli being isolated in her sputum, and she was medicated with antituberculous agents until December 1998.

On 4 April 1999, she was transplanted with a cadaveric kidney with two HLA matches on DR and a cold ischemia time of 12 hours. A triple immunosuppressive therapy was begun with cyclosporine, prednisone, and azathioprine. There was an immediate diuresis with a rapid decline of serum creatinine (Scr). She was medicated with isoniazid for tuberculosis prophylaxis. There was a slight rise of hepatic transaminases (two to three times the reference value) while she was in the hospital, which persisted in spite of the reduction on isoniazid dosage (300 to 150 mg/day). She was discharged on the ninth day with an Scr of 1.5 mg/dL.

On her first outpatient visit, she complained of tiredness, and we noticed a hyperpigmented skin. In addition, the evolution of several hematological and biochemical parameters was surprising: there was not just a rise of hemoglobin, but also of serum fast glycemia and of serum transaminases, as well as of both serum fast transferrin saturation and ferritin (Table 1). In the face of this clinical and laboratorial data, we considered hemochromatosis as the most likely diagnosis and ordered several exams to confirm it. The abdominal CT scan showed evidence of a slightly enlarged but hyperdense liver. Its biopsy showed abundant iron deposits within the hepatocytes, compatible with the diagnosis of hemochromatosis. The hepatic iron concentration was found to be 384 μmol/g of dry weight (normally less than 36 μmol/g). The calculated hepatic iron index (hepatic iron concentration/patient's age) was 5.8, the norm being 1 or less and values equal to or greater than 1.9 were found in hereditary hemochromatosis.[3,6] The echocardiogram showed moderate concentric ventricular hypertrophy, good systolic function, and fibrosed nodule on the aortic valve. We were not able to investigate her past family history, and her only living daughter has no signs of the disease.

Table 1. Laboratorial Evolution Before and After Kidney Transplantation

	Renal Transplantation			
	1997	1998	4/16/99	5/18/99
Hb (g/dL)	8.3–12.3	8.4–13.2	10.1	15.4
TGO (U/L)	31–55	17–40	118	58
TGP (U/L)	45–115	21–90	219	125
Fe (mg/dL)	81–84	160–181	128	228
Transf sat (%)	50–65	57–95	60	77
Ferritin (ng/mL)	1707–2332	3400–9590	13,664	11,190
Glycemia (mg/dL)	78–90	76–92	91	176
Creat (mg/dL)			1.2	1.0

Her genetic study showed the presence of HLA A3, but was negative for the mutations in the HFE gene, namely C282Y and H63D.

On 1 June 1999, she was started on a weekly phlebotomy program, removing 350 mL of blood at each session, and she was started on subcutaneous rHuEPO (2000 U/week, about 30 U/kg/week), aiming to mobilize and remove parenchymal iron stores. To control diabetes, she began oral gliclazide. Since then, transferrin saturation and ferritin have been decreasing. Also, diabetes has been easier to control and transaminases have reached normal values. This evolution is shown in Table 2. Fatigue complaints have disappeared, and her skin hyperpigmentation is less marked.

DISCUSSION

Hemochromatosis is a genetic disease in which mutations in the HFE gene, first described in 1996,[3] cause increased intestinal iron absorption. This gene is located on the short arm of chromosome 6, near the HLA A locus. It is believed

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Table 2. Laboratorial Data Before and After Hemapheresis and rHuEPO Therapy

	5/18/99	7/2/99	8/10/99	11/23/99
Hb (g/dL)	15.4	12.7	12.3	12.9
TGO (U/L)	58	33	35	28
TGP (U/L)	125	76	61	44
Fe (mg/dL)	228	182	225	133
Transf sat (%)	77	74	76	35
Ferritin (ng/mL)	11,190	9840	5756	2500

Therapy was begun on 1 June 1999.

that it codifies a protein that is involved in the regulation of intestinal iron absorption.[7] Iron is primarily deposited in parenchymal cells, in contrast to what happens in hemosiderosis where iron is deposited mainly in the reticuloendothelial system. The clinical manifestations include alterations in liver function, fatigue and lethargy, skin hyperpigmentation, diabetes mellitus, arthralgia, impotence and loss of libido, cardiac insufficiency, and conduction defects on the ECG.[1,2,6,8] Diagnosis relies on the demonstration of iron overload in the absence of either a heavy transfusional history or therapy with high doses of parenteral iron. This can be accomplished through blood analysis (transferrin saturation higher than 45% and ferritin higher than 300 ng/mL)[6] or through a liver biopsy, which not only will show parenchymal iron but will also permit quantification of it. Indeed, values of 200 μmol of iron per gram of hepatic dry weight or higher have been associated with hepatic fibrosis or even cirrhosis.[9] In this way, the liver biopsy has a prognostic value as well. This patient showed the classical syndrome of iron overload associated with hepatic dysfunction and bronze diabetes, so the diagnosis of hemochromatosis was very likely. Although the search for known mutations in the HFE gene was negative, she was HLA A3 positive. This locus was formerly related to hemochromatosis, before the discovery of HFE gene.[10] Homozygosity for the C282Y mutation, a cysteine to tyrosine substitution at amino acid 282, is responsible for typical hemochromatosis in 85 to 90% of the patients of northern European descent.[5] Another mutation, H63D, which consists in the substitution of aspartate for histidine at amino acid 63, may contribute to increased hepatic iron stores, but does not appear to lead to overt hemochromatosis in the absence of the former mutation.[3,4] Some patients with the clinical, biochemical, and histopathological criteria of hemochromatosis show neither of these mutations.[3,6,11] It also seems to be the case in this patient.

Only after renal transplantation did the full-blown clinical picture of hemochromatosis become clear in our patient. We could not find an exact reason for this, although the absence of hemodialysis, with its accompanying and unavoidable small repeated phlebotomies, may have played a role. Once under dialysis, other factors, such as kidney failure-associated anaemia related mainly to decreased endogenous production of erythropoietin, could also have had a part. In this way, the normalization of the endocrine renal function through the kidney allograft would have caused the full expression of this disease. In addition, the inflammatory condition that surrounds the insertion of a kidney allograft may have had a contributory place. Finally, the immunosuppressive therapy itself may eventually have interfered with the iron metabolism in our patient.

The few cases concerning hemochromatosis and renal transplantation that we were able to find in the medical literature are from the early 1980s, before rHuEPO therapy was available, when patients on dialysis were often transfused and iron overload was common. Also, by that time other causes of hepatic dysfunction such as hepatitis C were frequently underdiagnosed. In those patients, sepsis and hepatic insufficiency were considered the main causes of death.[12–14]

Although our patient had all the criteria of heavy iron overload, our therapy approach, regular hemapheresis, and rHuEPO can be considered, for the first 6 months, to be successful.

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