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Cardiac transplantation due to hemochromatosis. A pediatric case report

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ABSTRACT

Hemochromatosis is a disease characterized by excess iron stores in multiple organs, including the liver, pancreas, skin, and heart. The infiltration of the heart is an important factor in morbidity and mortality. Here we describe the case of a pediatric patient with end-stage heart failure who required a heart transplantation, with no complications. After the surgery, she showed biochemical and clinical improvement, with a positive impact on her quality of life and a prolonged survival.

Key words: *hemochromatosis; cardiac transplantation; iron overload; dilated cardiomyopathy; heart failure.*

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INTRODUCTION

Hemochromatosis is a syndrome characterized by excess iron stores. Primary or hereditary hemochromatosis (HH) is an autosomal recessive disorder associated with a mutation of the *HFE* gene located on chromosome 6. It has an estimated population incidence of 0.1% to 0.5%. Secondary hemochromatosis, instead, occurs as a consequence of iron overload caused by another condition, such as certain types of anemia, repeated blood transfusions, long-term hemodialysis, or chronic liver disease.[1,2]

This diseases predisposes to iron overload cardiomyopathy (IOC), which may be described as dilated or restrictive and may eventually progress to end-stage heart failure, warranting an advanced management, such as heart transplantation,[3,4] as reported in the case described here.

CASE REPORT

This was a 10-year-old, female patient referred to our hospital with a diagnosis of heart failure, uncontrolled hyperglycemic metabolic state, and acute renal failure. She was admitted due to acute abdominal pain, progressive orthopnea for the past 48 hours, and decreased diuresis.

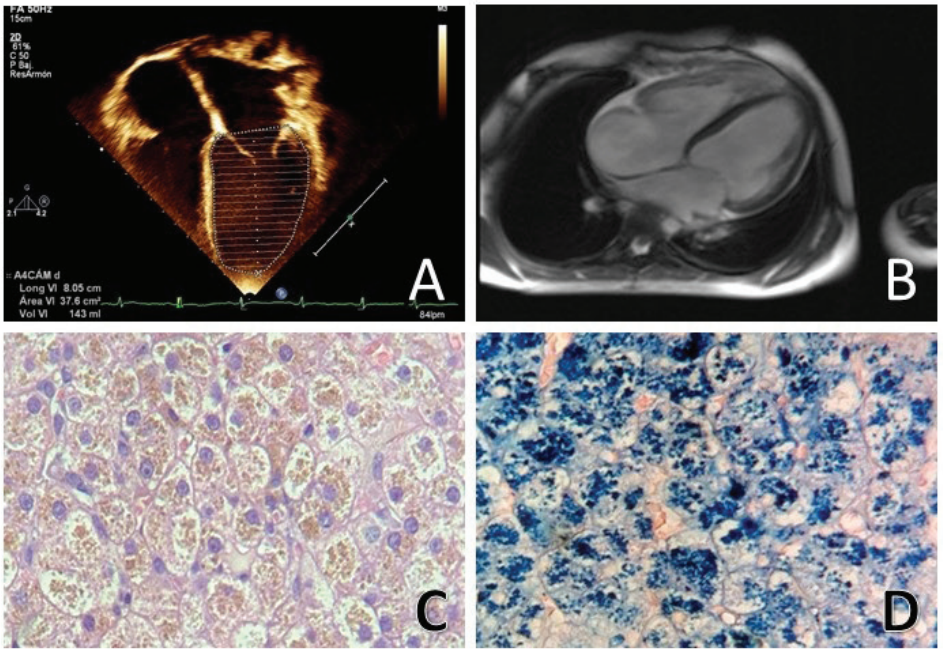
Her medical history included a diagnosis of type I diabetes mellitus, which debuted with ketoacidosis 3 months prior to her current condition. Her physical examination revealed she had hyperpigmented macules in her skin. She was found to have tachypnea, with baseline crepitant rales and hyperdynamic precordium, class III according to the New York Heart Association (NYHA) functional classification, and hepatomegaly at 7 cm from the right costal arch.

The following were observed in specialized tests: left bundle-branch block in the electrocardiogram, cardiomegaly at the expense of the left ventricle (LV), bilateral pleural effusion, and increased pulmonary flow in the chest X-ray. The echocardiogram showed a dilated vena cava, moderate mitral regurgitation, and left ventricular ejection fraction (LVEF) of 15% (*Figure 1A*).

The magnetic resonance imaging (MRI) showed global hypokinesis with greater involvement of the apical and mid inferolateral and anterior wall of the LV, global hypokinesis of the right ventricle, LVEF of 17%, right ventricular ejection fraction of 21%, biventricular dilated cardiomyopathy, patchy enhancement, with epicardial and endocardial involvement at the inferoseptal and lateral level at the mid LV. The type of relative and late enhancement, as well as patchy enhancement, is positive for myocarditis and bilateral pleural effusion (*Figure 1B*).

The viral panel resulted negative, and an

Figure 1. (A) Echocardiogram showing cavity dilation. (B) Magnetic resonance imaging showing biventricular dilated cardiomyopathy. (C) Hepatocytes with abundant golden-brown pigment, hematoxylin and eosin staining. (D) Positive Perls' Prussian blue stain.



infectious myocarditis was ruled out. Given that hemochromatosis was suspected, a test protocol was initiated. The iron kinetics assessment showed free iron: 318 mcg/dL, ferritin: 13 400 µg/L, transferrin: 2.42 g/L, soluble transferrin receptor: 0.817, and transferrin saturation: 96%. The liver and biliary tract ultrasound showed bile duct dilatation at the level of the common bile duct and a hepatopetal flow velocity in the portal vein of 10.7 cm/s.

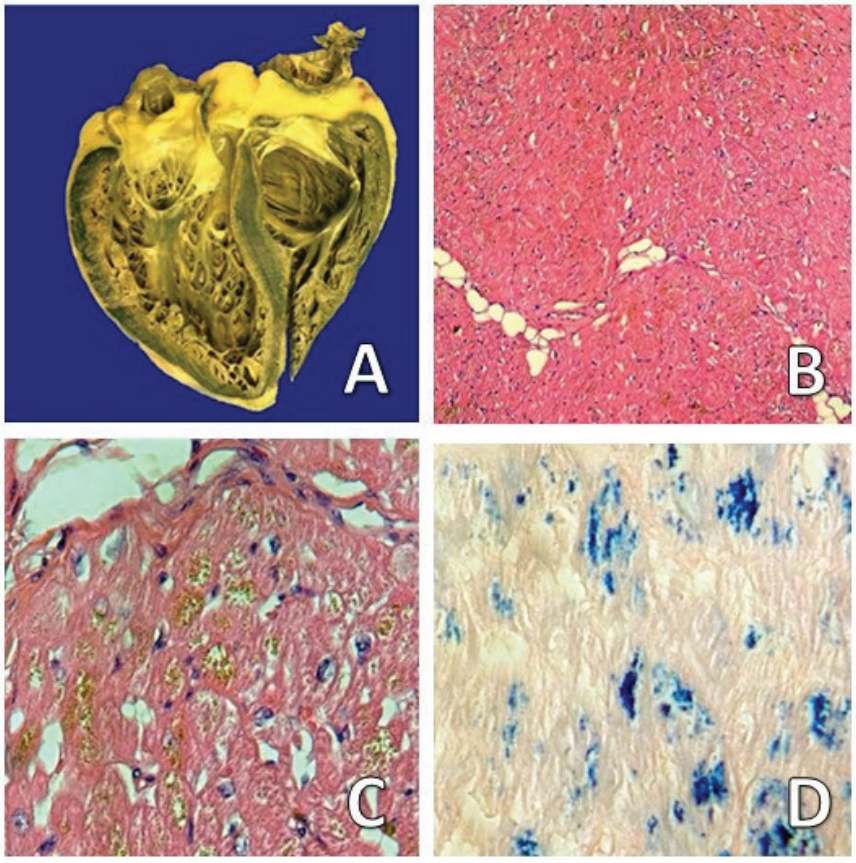
The needle biopsy of the liver revealed fibrosis, increased inflammatory infiltrate without activity, and enlarged hepatocytes with abundant golden-brown pigment in the lobule, positive for the Perls' Prussian blue stain. These findings were compatible with the diagnosis of hemochromatosis (*Figures 1C* and *1D*).

A medical treatment with iron chelation therapy and phlebotomy was initiated. However, the patient was re-admitted several times due to refractory heart failure, so she was listed for heart transplantation. After 7 months on the waiting list, she underwent an orthotopic heart transplantation using the bicaval approach. The main surgical findings were dilated cardiomyopathy, cardiomegaly, poor contractility, and orange-colored tissue.

After the transplantation, the echocardiogram showed a LVEF of 65%. The pathological study of the explanted heart showed an altered morphology, dilated at the expense of the ventricles, a brown surface with punctate hemorrhage, thickened valves, and brown-orange myocardium. The microscopic examination revealed fibroelastosis and cardiomyocyte hypertrophy, with deposits of coarse granules of hemosiderin that were also observed in the interstitium. The integrated diagnosis was dilated cardiomyopathy due to hemochromatosis (*Figure 2*).

One week after the surgery, the first post-transplantation endomyocardial biopsy was performed, which showed acute mild rejection (1R) (interstitial and/or perivascular

Figure 2. (A) Explanted heart. Macroscopic image. (B and C) Hematoxylin and eosin microscopic images, cardiomyocytes with granular ocher pigment inside. (D) Perls' Prussian blue stain showing iron deposition



infiltrate with up to 1 focus of myocyte injury) according to the grading criteria for acute cellular rejection of the International Society for Heart and Lung Transplantation. The second endomyocardial biopsy was performed 1 month after the transplantation and acute 1R cellular rejection persisted, with negative Perls' Prussian blue stain. The patient's course was good, without complications, so she was discharged from the hospital.

In the follow-up of hemochromatosis, she continued with iron chelation therapy based on deferoxamine and her test values decreased sharply and progressively in repeated iron kinetics assessments; she did not require management with phlebotomies. After 18 months, a new endomyocardial biopsy showed minimal regenerative changes, with negative special stains for hemosiderin. Four years after the transplantation, the iron kinetics values continue to be within normal parameters and, in turn, the patient reports clinical improvement.

DISCUSSION

Here we describe the multidisciplinary approach required for the diagnostic and therapeutic process of a patient with hemochromatosis, as it is a disease with multiple organ involvement. Cardiomyopathy is a significant risk factor for mortality and morbidity.

Iron deposition in multiple systems results in typical manifestations, such as liver disease, skin hyperpigmentation, diabetes mellitus, and heart failure.[2] However, the early symptoms of hemochromatosis are often non-specific and go undiagnosed until significant target organ failure has developed.[1] Our patient presented the whole clinical spectrum, which led to a high level of disease suspicion and a test protocol was initiated immediately.

In relation to diagnostic methods, the electrocardiogram allows detecting abnormalities of the conduction system due to iron infiltration. The echocardiogram is the most commonly used tool, and early findings typically include LV diastolic dysfunction with a restrictive filling pattern that progresses to dilated cardiomyopathy with decreased LVEF.[2,5] The MRI is the technique that allows a qualitative assessment of myocardial iron load.[2]

As for the histopathological diagnosis, given the suspicion of IOC, it was decided to perform a liver biopsy, because iron deposition occurs significantly faster in this organ, thus excluding the need for an endomyocardial biopsy.[2]

The study of mutations in the *HFE* gene confirms the diagnosis of HH.[2] In the case of our patient, it was not done because it was not available.

The first-line medical treatment is based on phlebotomy, although iron chelation therapy is preferred in patients with anemia or hemodynamic instability.[2]

In the face of conventional therapeutic failure, a heart transplantation is the best alternative to improve the survival and quality of life of patients with end-stage IOC. However, it does not stop the natural course of the disease. Therefore, phlebotomy and chelation therapy should be continued to prevent the infiltration of the transplanted heart,[3] and follow-up should be based on periodic iron kinetics assessment and hemoglobin level monitoring to prevent secondary anemia. In our patient, the iron chelation therapy was enough to achieve adequate values.

There is scarce bibliography on patients who required a heart transplantation due to hemochromatosis after ceasing to be candidates for conservative management, especially in the pediatric population. We believe that a higher level of reporting of similar cases would greatly benefit the assessment of the survival and quality of life of these patients. ■

REFERENCES

1. Schofield RS, Aranda JM Jr, Hill JA, Streiff R. Cardiac transplantation in a patient with hereditary hemochromatosis: role of adjunctive phlebotomy and erythropoietin. *J Heart Lung Transplant.* 2001; 20(6):696-8.
2. Bejar D, Colombo PC, Latif F, Yuzefpolskaya M. Infiltrative Cardiomyopathies. *Clin Med Insights Cardiol.* 2015; 9(Suppl 2):29-38.
3. Caines AE, Kpodonu J, Massad MG, Chaer R, et al. Cardiac transplantation in patients with iron overload cardiomyopathy. *J Heart Lung Transplant.* 2005; 24(4):486-8.
4. Robinson MR, Al-Kindi SG, Oliveira GH. Heart and heart-liver transplantation in patients with hemochromatosis. *Int J Cardiol.* 2017; 244:226-8.
5. O'Glasser AY, Scott DL, Corless CL, Zaman A, et al. Hepatic and cardiac iron overload among patients with end-stage liver disease referred for liver transplantation. *Clin Transplant.* 2010; 24(5):643-51.