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MYOCARDITIS AND CARDIOMYOPATHY

Early diagnosis of hemochromatosis-related cardiomyopathy with magnetic resonance imaging

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The hallmark of hemochromatosis is the deposition of iron in multiple tissue types, most notably the skin, liver, pancreas, thyroid, and heart. Definitive diagnosis of iron deposition generally requires invasive methods, such as direct tissue biopsy. We describe a 40 year-old woman with end-stage liver disease secondary to hereditary hemochromatosis and alcohol abuse, who was referred to the cardiology service as part of an evaluation for orthotopic liver transplant. The patient had no cardiac history but a dobutamine stress echocardiogram, performed as a portion of the pre-operative cardiac evaluation, could not be completed due to intermittent, supraventricular tachycardia. Additional cardiac testing, including electrocardiography and resting echocardiography, raised suspicion for cardiomyopathy related to hemochromatosis but was non-diagnostic. Cardiac magnetic resonance (MR) of this patient revealed deposition of iron in the myocardium and established the diagnosis of hemachromatosis-related cardiomyopathy. These findings suggest that cardiac MR may be more sensitive than other non-invasive, diagnostic tools in the initial evaluation of hemochromatosis-related cardiomyopathy and may be used as an alternative to myocardial biopsy. We propose that conventional T1- and T2-weighted spin echo MR sequences can be used routinely as non-invasive modalities to assess the presence of iron deposition in the tissues of patients with hemochromatosis.

Key Words: Magnetic resonance imaging; Hemochromatosis; Cardiomyopathy

1. Introduction

Hereditary hemachromatosis is an autosomal recessive disorder caused by a series of mutations in the HFE gene, leading to increased intestinal absorption of iron. Elevated serum iron, transferrin saturation, and ferritin eventually lead to iron deposition in many tissue types, most notably the skin, liver, pancreas, thyroid, skin, and heart. The prevalence of homozygous carriers of HFE mutations is 5–8/1000 among people of European descent (1, 2). Not all carriers of the mutation present with signs and symptoms consistent with tissue destruction secondary to iron deposition. It is thought that environmental factors, notably other illnesses, play an important role in the development of clinical hemochromatosis. Affected individuals typically do not present with clinical evidence of tissue iron deposition until middle age (3, 4). The sentinel sign of disease is skin pigmentation. Some patients also present with abnormal liver function tests. As the disease progresses, patients can develop cirrhosis, diabetes mellitus, hypothyroidism, and dilated cardiomyopathy, based on the usual pattern of tissue deposition described above. The combination of skin pigmentation and diabetes mellitus led to the previous description of this disorder as "bronze diabetes."

Destruction of tissue secondary to iron deposition is frequently difficult to document with non-invasive methods. Definitive diagnosis requires verification of iron deposition in affected organs. Previously, invasive methods such as direct biopsy were required, as iron deposition is frequently difficult to document with most non-invasive methods (5).

Recent reports in the literature have described the utility of MR in the quantitation of iron deposition in tissues, most notably in patients with thalassemia (6–10). These studies have exhibited the ability of customized cardiac MR (CMR) sequences to assess the levels of iron in solid organs longitudinally. We report here a case of hereditary hemochromatosis where early diagnosis of hemochromatosis-related cardiomyopathy was determined with a conventional CMR sequence.

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2. Report of a case

A 40-year-old woman with a history of alcohol abuse presented with a two year history of fatigue and progressive darkening of skin. During the three months prior to admission

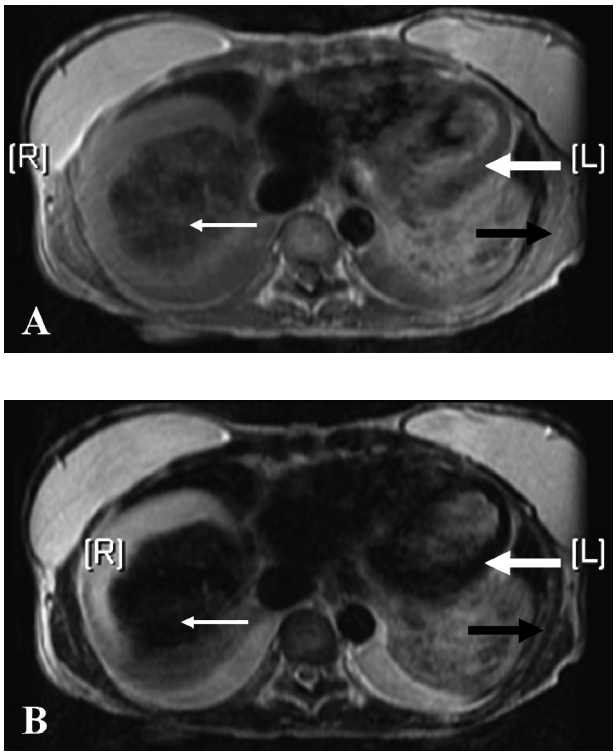

Figure 1. A. T1-weighted, SE image in axial plane. Attenuation of signal in left ventricular myocardium (large white arrow) and superior pole of liver (small white arrow) suggests iron deposition in contrast with signal for skeletal muscle (black arrow). T1-weighted sequence obtained with double inversion recovery SE: TE 20, echo trail length (ETL) 32, bandwidth (BW) 62.5, FOV 36, matrix = 256 × 256. B. T2-weighted, SE image in identical axial plane as Fig. 1A. Significant signal attenuation is seen in myocardium, as compared to skeletal muscle. This T2-weighted sequence obtained with double inversion recovery SE: TE 80, ETL 32, BW 62.5, FOV 36, matrix = 256 × 256.

to our hospital, the patient had been admitted to outside hospitals several times with these complaints and was found to have anemia; three separate transfusions with packed red blood cells were performed. Pertinent findings on initial physical exam at our hospital included evidence of encephalopathy, jaundice, and shifting dullness in the abdomen suggesting significant accumulation of ascites. Pertinent laboratory values included abnormal liver function tests and evidence of poor liver synthetic function (AST 57, ALT 31, total bilirubin 9.6, alkaline phosphatase 59), most notably low albumin, total protein (2.0 and 5.1, respectively), and coagulopathy (INR 2.3, PT 26.1, PTT 56.7). The patient's complete blood count revealed only anemia (white blood cell count 4.7, hemoglobin 10.3, hematocrit 29.5, platelet count 62). Blood chemistry analysis and thyroid function studies did not reveal any abnormalities. Screening tests for the Hepatitis A, B, and C viruses were negative. Abdominal ultrasound and CT scans revealed significant ascites but did not reveal any evidence of cirrhosis or abnormality in the biliary tree. The patient's family history was significant for hereditary hemochromatosis in her mother. In light of this family history and presentation with apparent liver failure, iron studies were performed. These studies revealed iron overload: total iron 120, ferritin 5520, and total iron binding capacity below measurable limit. Genetic testing for known HFE mutations was performed and revealed a homozygous H63D mutation (1, 11). Given the patient's coagulopathy, liver biopsy was considered to be imprudent and was therefore not performed. The patient's advanced liver failure and progressively worsening clinical status led to workup for orthotopic liver transplantation.

The patient had no cardiac history but a dobutamine stress echocardiogram, performed as a portion of the pre-operative cardiac evaluation, could not be completed due to intermittent junctional tachycardia. Twelve-lead electrocardiogram revealed diminished amplitude in the limb and precordial leads that did not meet the criteria for low voltage. Resting echocardiogram revealed mild left ventricular enlargement with left ventricular end-diastolic volume (LVEDV) of 132 mL and left-ventricular end-systolic volume (LVESV) of 65 mL. A mild reduction in left ventricular ejection fraction (LVEF) to 51% was also noted. No global or focal wall motion abnormalities were found during the resting or stress phases of the study. Pericardial effusion was not present. Mild to moderate tricuspid regurgitation was noted, with a right ventricular systolic pressure of 31 mmHg.

These findings raised suspicion for cardiomyopathy, but were inconclusive. Based on this patient's complex medical

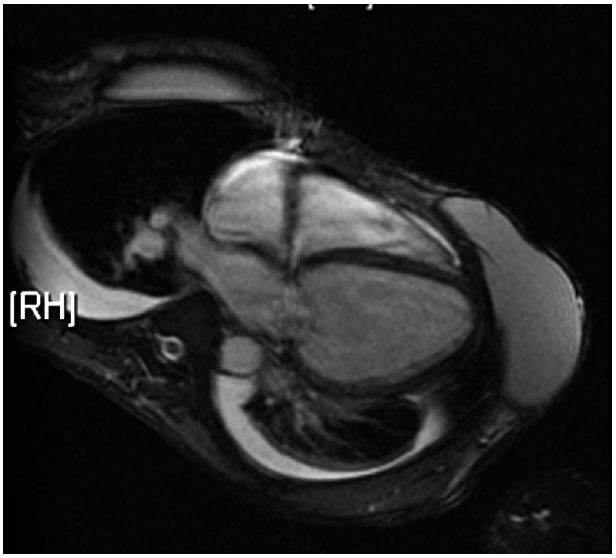

Figure 2. Four-chamber, long axis view obtained using SSFP (TE 1.6, flip angle 45, BW 125, FOV 36, matrix = 224 × 224). Attenuation of signal in the septum and the free walls of both ventricles is increased as compared to standard myocardial generated from SSFP imaging. These findings are consistent with the iron deposition pattern typically observed in histopathological analyses of cardiac hemochromatosis.

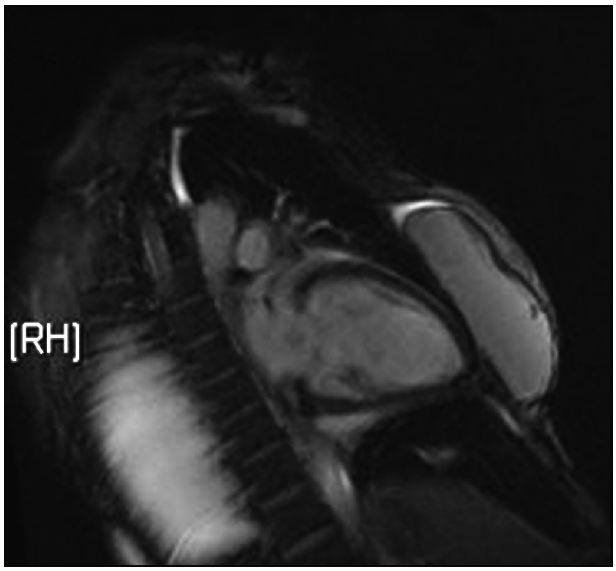

Figure 3. Two-chamber, long-axis view obtained using SSFP. Note homogeneous attenuation of signal throughout the thickness of the wall of the LV.

history, there was a broad differential diagnosis for cardiac dysfunction. In light of hemochromatosis in this patient, the presence of hemochromatosis-related cardiomyopathy could not be excluded. Echocardiography did not reveal evidence of other types of cardiomyopathy: there were no gross structural abnormalities, the appearance of the myocardium did not have a speckled appearance that may suggest amyloid deposition or infiltrative disease, and there was no obvious evidence of ischemic cardiomyopathy.

In an attempt to further characterize the nature of this putative cardiomyopathy, a series of magnetic resonance studies were conducted. Magnetic resonance was chosen due to its ability to detect iron with high specificity. All imaging was performed using a 1.5T GE Signa whole-body scanner (Milwaukee, WI). T1-weighted, double-inversion, spin-echo (SE) image was notable for abnormal attenuation of signal in myocardium and liver, and normal skeletal muscle signal (Fig. 1A). Further attenuation of myocardial and liver signal on T2-weighted SE image in comparison to normal skeletal muscle (Fig. 1B) was suggestive of iron deposition in the myocardium (12, 13). Skeletal muscle signal was attenuated to a much lower extent in the T2-weighted image, consistent with the relative sparing of non-cardiac, striated muscle in the early stages of hemochromatosis. The extent of liver signal attenuation was similar to myocardial signal attenuation, consistent with the natural history of the disease in this patient. The signal intensities measured from the T2-weighted SE images of the liver, myocardium, and skeletal muscle were 39, 43, and 52, respectively. Steady-state free precession (SSFP) sequences were also performed (parameters: TR 3.8, TE 1.6, slice thickness 10 mm, slice gap 0). Images obtained with the SSFP sequences demonstrated diffuse, homogeneous myocardial iron deposition in four-chamber (Fig. 2) and two-chamber (Fig. 3) images. SSFP short-axis cine images were also obtained in order to ascertain the dimensions of the left ventricle: LVEDV was 162.6 ml, LVESV was 75.2 ml. In addition, the stroke volume was 87.4 cc and LVEF was 53.8%. Signal-to-noise ratios (SNR) of the myocardium for the T1- and T2-weighted SE and the SSFP sequences were 5.6, 0.6, and 3.4, respectively (14).

The observed pattern of MR signal changes is best explained by myocardial iron deposition; therefore, it appears that hemochromatosis is the most likely etiology for the cardiomyopathy observed in this patient (13, 15). During the course of this evaluation, a simultaneous workup for orthotopic liver transplant was performed. The patient was denied a transplant due to history of poor compliance and failure to abstain from alcohol consumption. Liver failure progressed, and the patient expired several weeks after initial presentation.

3. Discussion

Up to one-third of patients with hereditary hemochromatosis present with cardiac morbidity, most notably a dilated cardiomyopathy caused by iron deposition in the myocardium. Definitive diagnosis of this type of cardiomyopathy is commonly made with direct myocardial biopsy, as most non-invasive methods cannot reliably document the presence of myocardial iron. Evidence from these non-invasive methods is indirect: diminution of voltages observed with twelve-lead electrocardiography is an associated but not a specific finding. Similarly, echocardiography in these patients will frequently reveal dilated cardiomyopathy but is not sensitive enough to reveal iron deposition in tissues.

Definitive diagnosis of iron deposition is important in patient management, as it determines the subsequent treatment strategy. This is particularly important in the case detailed above, as there were several plausible explanations for her cardiomyopathy. Myocardial biopsy is useful to this end but can be associated with significant morbidity. Invasive procedures of this type may be particularly dangerous in patients who are clinically unstable due to hepatic dysfunction.

Previous studies have shown that several MR methods can be used to quantitate iron deposition in several tissue types, most notably liver (6, 7) and cardiac tissue (8, 10). Several of these methods have been shown to be quite sensitive in the detection of iron deposition. In particular, the $T2^*$ method appears to be sensitive and highly specific, useful for quantitation and longitudinal tracking of iron deposition (8, 10). There are several reports describing the use of the $T2^*$ method in order to quantitate drops in myocardial iron deposition in thalassemia major patients undergoing iron removal therapy (9). Other techniques, including gradient echo and SSFP sequences could be useful to detect both $T2^*$ effects of iron deposition and wall motion simultaneously (6, 7).

In this study, specially designed T2* sequences were not used. Instead, we used conventional T1- and T2-weighted SE and SSFP sequences readily available on commercial MR scanners. These sequences revealed a highly specific signature for iron deposition in tissue: significant attenuation of myocardial signal in the T2-weighted spin echo images in comparison with the skeletal muscle signal and the marked attenuation of the myocardium in the SSFP images (11, 16). This attenuation pattern is not associated with normal myocardium nor is it associated with deposition of any other infiltrative disease of the myocardium. The conventional sequences were used, in part, to illustrate that the T2-weighted SE sequence is adequately sensitive for the assessment of iron deposition. The T2 and T2* sequences are both readily available and can be used routinely by clinicians to make initial assessments of iron deposition.

Our case study shows that conventional cardiac MR sequences may assist in the initial diagnosis of cardiomyopathy due to iron deposition. This is in agreement with the experience of other centers (17). In addition, previous studies have shown that cardiac MR can provide comprehensive information, including an assessment of stress-induced ischemia, viability, and quantitative resting LVEF, which may eliminate the need for multiple diagnostic modalities. We conclude that cardiac MR can be used as a non-invasive alternative to biopsy in patients with cardiomyopathy suspected to be secondary to hemochromatosis.

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