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Endomyocardial Biopsy in Hemochromatosis: Clinicopathologic Correlates in Six Cases

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Clinical and pathologic features of cardiac hemochromatosis diagnosed by endomyocardial biopsy in six men, aged 32 to 75 years (mean 52), are described. Echocardiography demonstrated left ventricular enlargement and marked global systolic dysfunction in five. Cardiac catheterization demonstrated normal coronary arteries, increased left ventricular end-diastolic pressure and decreased left ventricular systolic function in all five so studied. Stainable iron was present in all endomyocardial biopsy specimens from the five patients with decreased left ventricular systolic function. Histologically, iron was detected only within the sarcoplasm, and its extent varied inversely with ventricular function.

Thus, cardiac hemochromatosis represents a storage rather than an infiltrative disease. These results indicate that stainable iron is consistently observed in endomyocardial biopsy specimens from patients with impaired left ventricular systolic function. Iron staining is recommended for endomyocardial biopsy specimens from patients with idiopathic cardiac dysfunction.

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In systemic iron overload disorders, the association between histologically demonstrable myocardial iron and cardiac dysfunction has been described in autopsy studies (1) but only rarely in studies based on cardiac biopsy or surgical specimens from living patients (2–4). Thus, the role of endomyocardial biopsy in the evaluation and management of cardiac hemochromatosis has not been defined. The antemortem diagnosis of cardiac hemochromatosis usually has been presumptive, based on findings of heart failure associated with clinical and laboratory evidence of iron overload with or without improved cardiac function after periodic phlebotomy or chelation therapy (5–10). In some patients, cardiac failure is the sole or predominant manifestation of iron overload (7,11), and cardiac involvement is the leading cause of death in this disorder (12,13). With these considerations in mind, this study was undertaken to describe clinicopathologic correlations in six patients with cardiac hemochromatosis documented by endomyocardial biopsy.

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Methods

Study patients. Among 642 endomyocardial biopsy specimens interpreted at our institution by one of us (W.D.E.) between 1977 and 1986, six patients with cardiac hemochromatosis were identified by the presence of stainable iron in the myocardium. These patients constituted the study group. All patients had undergone echocardiographic examination, and five of the six had been studied by cardiac catheterization including left ventriculography and coronary arteriography. Three patients also had undergone right heart catheterization. For each of the patients in the study group, the clinical history, endomyocardial biopsy tissue, chest radiographs, electrocardiograms, echocardiograms and cardiac catheterization data were reviewed.

Endomyocardial biopsy. In all patients, three to five endomyocardial samples were obtained (right ventricular in five and left ventricular in one). Biopsy specimens were fixed in 10% neutral buffered formalin, processed routinely for light microscopy and stained with hematoxylin-eosin, sulfated alcian blue, Masson's trichrome, and Gomori's iron stains. The location of stainable iron was recorded, and the

Table 1. Clinical Features of Six Patients With Cardiac Hemochromatosis

Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (yr)/gender	32/M	33/M	46/M	55/M	69/M	75/M
Hemochromatosis	Genetic	Genetic	Genetic	Genetic	Acquired	Acquired
Associated disease	Familial hemolytic anemia; alcohol abuse	Hereditary spherocytosis	None	None	Sideroblastic anemia	Sideroblastic anemia
Duration of symptoms (mo)	1	8	18	1	12	6
Presenting symptom(s)	Dyspnea	Dyspnea	Dyspnea	Dyspnea	Dypsnea, arthralgias	Dyspnea
Chest radiograph	Cardiomegaly	Cardiomegaly	Cardiomegaly	Cardiomegaly	Cardiomegaly	Cardiomegaly
Electrocardiogram	T-Wave abnormality	Long QT	1° AVB, LAD, AS & inf Q waves	AF, LAD	LAD	AF
Echocardiogram						
WTh (mm) (8 to 12)	11	8	10	11	10	11
EDD (mm) (40 to 54)	60	68	62	60	66	50
EF (%)	16	32	24	15	20	61
Cardiac catheterization						
Hemodynamics						
LVEDP (mm Hg)	29	18	21	18	16	—
RVEDP (mm Hg)	19	—	—	9	16	—
PCWP (mm Hg)	18	—	—	12	14	—
Angiography						
Coronary arteries	Normal	Normal	Normal	Normal	Normal	—
Ventriculogram	Severe LV hypokinesia	Severe LV hypokinesia	Severe LV hypokinesia	Severe LV hypokinesia	Severe LV hypokinesia	—
EDVI	130	174	144	—	87	—
ESVI	96	102	108	—	64	—
EF (%)	25	41	24	45	26	—
Survival since biopsy (mo)	7	2 (died)	8	6	8	39

AF = atrial fibrillation; AS = anteroseptal; AVB = atrioventricular block; EDD = end-diastolic diameter; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; inf = inferior; LAD = left axis deviation; LVEDP = left ventricular end-diastolic pressure; M = male; PCWP = pulmonary capillary wedge pressure; RVEP = right ventricular end-diastolic pressure; WTh = wall thickness (expressed as mean wall thickness of ventricular septum and left ventricular posterior walls; values in parentheses denote the normal range).

degrees of stainable iron and collagen formation were expressed as a grade of tissue involvement (normal = 0%, grade 1 = 1 to 25%, grade 2 = 26 to 50%, grade 3 = 51 to 75% and grade 4 = >75%). These determinations were performed by one of us (W.D.E.) without knowledge of clinical information.

Results

General features (Table 1). All six patients were men; their ages ranged from 32 to 75 years (mean 52). Four had genetic hemochromatosis diagnosed by standard clinical and laboratory criteria (12) including liver biopsy in three. The two youngest patients also had concurrent familial anemia. Two other patients had hemochromatosis associated with sideroblastic anemia; each also had undergone liver biopsy. No patient had a history of transfusion. One patient (Case 5) had taken iron orally for 2 years.

Symptoms and survival. Dyspnea was a presenting symptom in all six patients and was associated with physical signs of congestive heart failure in five. Five patients are alive; one died of ventricular fibrillation 3 months after diagnosis. Of the five surviving patients, the three with genetic hemochromatosis continue to undergo periodic phlebotomy. Each of the five is also being treated with digitalis and diuretics.

One patient (Case 1) admitted to heavy alcohol use; he was advised to abstain from alcohol, and subsequent echocardiographic examination demonstrated normalization of left ventricular systolic function before initiation of a phlebotomy regimen.

Laboratory findings (Table 2). Indicators of iron overload, including transferrin saturation and ferritin concentration, were abnormal in all six patients. The serum iron concentration, however, was normal in four of the six.

Liver biopsy, performed in five patients, demonstrated severe hemosiderosis in all and cirrhosis in three. Quantitation of elemental iron by atomic absorption spectroscopy in hepatic biopsy tissue demonstrated heavy iron overload in four of these five. In one patient (Case 4) with suspected genetic hemochromatosis, liver biopsy was not performed because histologic demonstration of iron overload was obtained on endomyocardial biopsy.

Table 2. Laboratory Features of Six Patients with Cardiac Hemochromatosis

Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Hemoglobin (g/dl)/hematocrit (%)	12.6/37.0	15.8/44.2	15.6/44.4	15.4/—	8.8/26.5	9.8/28.6
Serum iron (μg/dl) (75 to 175)*	209	172	147	133	170	300
Total iron-binding capacity (μg/dl) (240 to 450)	216	185	171	—	198	300
Percent saturation (18 to 50%)	97	93	86	—	86	100
Serum ferritin (μg/liter) (20 to 300)	1,300	2,500	2,840	3,898	2,220	522
Hepatic histologic findings						
Hemosiderosis	Severe	Severe	Severe	—	Severe	Severe
Cirrhosis	No	Yes	Yes	—	Yes	No
Hepatic iron concentration (μg/g dry weight) (530 to 900)	20,292	21,233	22,969	—	12,025	NA

*Values in parentheses indicate normal range.

Cardiomegaly was observed by chest radiography in five of the six patients. Electrocardiography demonstrated nonspecific abnormalities in all six patients (Table 1).

Two-dimensional echocardiography, performed in all patients, demonstrated left ventricular dilation and severe systolic dysfunction in five. The sixth patient had a normal-sized left ventricle with an ejection fraction of 61%. Ventricular wall thickness was normal in all patients, and no patient had regional wall motion abnormalities.

Cardiac catheterization was performed in five of the six patients, and all five had increased left ventricular end-diastolic pressure. Ventriculography revealed left ventricular enlargement and severe hypokinesia, and coronary angiography demonstrated normal coronary arteries in all five patients. One patient (Case 5) with severe left ventricular hypokinesia and normal coronary arteries had equalization of increased left and right ventricular end-diastolic pressures.

Endomyocardial biopsy (Table 3). Light microscopic examination of endomyocardial biopsy tissue that was stained for iron revealed sarcoplasmic iron in all six patients (Fig. 1). Iron was not observed within other types of cells or in extracellular spaces. Although the severity of iron deposition varied from minimal to severe among the six patients, it tended to be consistent within biopsy specimens from individual patients. Furthermore, the histologic severity was directly related to the degree of left ventricular dysfunction (Fig. 2).

Although the data suggest that a correlation may exist between left ventricular function and grade of stainable iron in endomyocardial biopsy specimens, the small sample size precluded a demonstration of statistical significance (Spearman's rank correlation coefficient = −0.80; $p = 0.08$). In one patient (Case 6) with normal left ventricular systolic function, myocardial iron deposition was observed in only one of four endomyocardial biopsy specimens. Variation in severity of iron deposition by anatomic site in individual patients and among different patients has been described previously in autopsy hearts from patients with hemochromatosis (14).

Fibrosis was present in endomyocardial biopsy specimens from all patients; it was minimal in five cases and mild in one (Table 3). Similar observations were reported in an autopsy study of cardiac hemochromatosis (14).

Discussion

Diagnosis of hemochromatosis. Cardiac hemochromatosis should be considered in any patient with unexplained heart failure. Screening for systemic iron overload includes determination of transferrin saturation and ferritin concentration in serum. The combined specificity and sensitivity of these two screening tests is approximately 95% for the detection of

Table 3. Histopathologic Features of Endomyocardial Biopsy Tissue From Six Patients With Cardiac Hemochromatosis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Specimens with iron/total specimens	5/5	4/4	5/5	3/3	5/5	1/4
Myocellular						
Iron (grade)*	3	2	4	4	2	1
Hypertrophy	Mild	Moderate	Mild	Moderate	Moderate	Mild
Degeneration	Moderate	Minimal	Severe	Minimal	Minimal	Mild
Interstitial fibrosis (grade)*	2	1	1	1	1	1

*Normal = 0%, grade 1 = 1 to 25%, grade 2 = 26 to 50%, grade 3 = 51 to 75%, grade 4 = >75%.

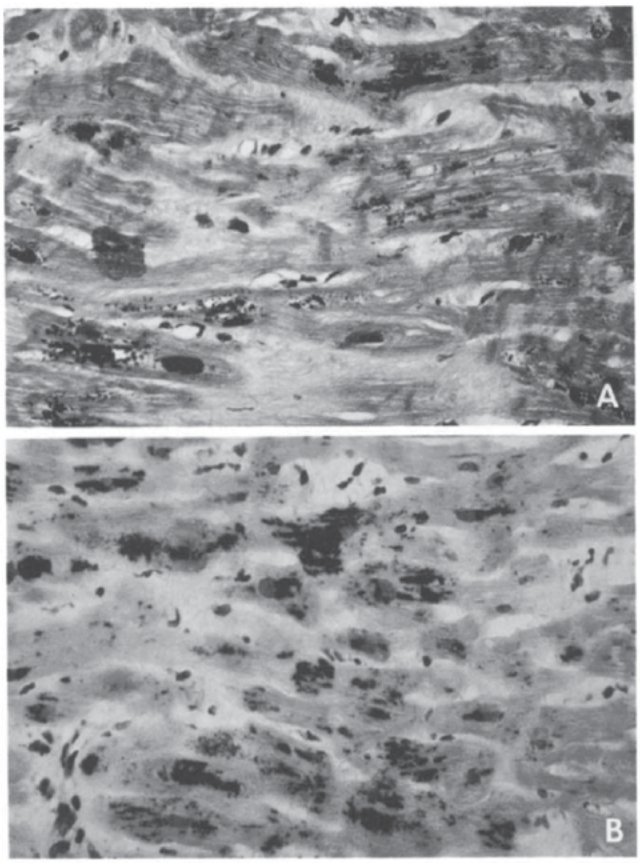
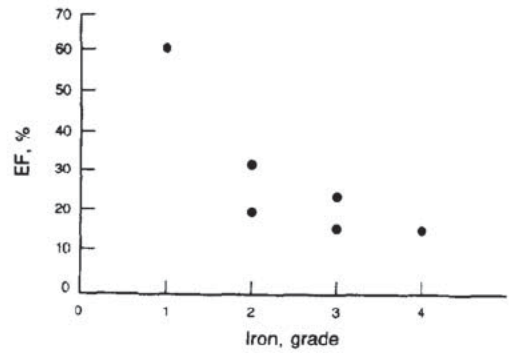


Figure 1. Variation in quantity of stainable iron deposition in endomyocardial biopsy tissue in two cases. Iron accumulation is limited to myocytes and tends to be perinuclear. **A**, Mild (grade 2); **B**, severe (grade 4). (Gomori iron; original magnification ×100, reduced by 33%.)

iron overload in patients with genetic hemochromatosis (15). In contrast, serum iron concentration is not as reliable (15).

If screening test results are consistent with iron overload, histologic confirmation of hemochromatosis is necessary. Generally, this has been accomplished by liver biopsy. Endomyocardial biopsy, however, may be indicated in patients whose primary clinical manifestations are cardiac in origin. Furthermore, in experienced hands, transvenous right ventricular endomyocardial biopsy may be safer than percutaneous liver biopsy (16–18).

Figure 2. Inverse relation between left ventricular ejection fraction (EF) and grade of deposition of stainable iron in six cases of hemochromatosis. This relation was not statistically significant (Spearman's rank correlation coefficient = −0.80; p = 0.08).



Cardiac involvement in hemochromatosis. The hemodynamic and morphologic abnormalities of cardiac hemochromatosis have been described as either dilated (2,5) or restrictive (3) [cardiomyopathy]. Of the five patients with systolic functional abnormalities in this report, each had a dilated left ventricle and increased left ventricular end-diastolic pressure. No patient had the classic findings of restriction. Early cardiac involvement by hemochromatosis, however, may be manifested by diastolic or restrictive dysfunction.

In a previous echocardiographic study (19), the authors suggested that increased wall thickness may be a feature of secondary posttransfusional hemochromatosis. However, others (8,9,14,20) have reported normal wall thickness in patients with nontransfusional hemochromatosis and cardiac dysfunction. In this study, all patients had normal ventricular wall thickness as assessed by echocardiography. Accordingly, increased ventricular wall thickness does not appear to be a feature of nontransfusional cardiac hemochromatosis.

Endomyocardial biopsy in hemochromatosis. The microscopic features of endomyocardial biopsy tissue from four adolescents with transfusion-related hemochromatosis have been described (4). However, only one patient had cardiac dysfunction as determined by cardiac catheterization. Furthermore, in only one patient was abnormal accumulation of myocardial iron demonstrated, and this patient had normal cardiac function. These observations led the investigators (4) to conclude that endomyocardial biopsy is an insensitive method for the determination of *early* myocardial iron deposition in *transfusion-related* hemochromatosis associated with thalassemia major.

In contrast, the histopathologic characteristics of biopsy tissue from patients with *nontransfusional* cardiac hemochromatosis have been described in only two living patients (2,3); moreover, in one of these patients, biopsy tissue was obtained at pericardiectomy because the patient was presumed to have pericardial constriction. Observations from the current investigation of six patients suggest that histologically demonstrable myocardial iron is a consistent finding in endomyocardial biopsy tissue from patients with *nontransfusional* iron overload and associated cardiac dysfunction. Although cardiac iron deposition in hemochromatosis tends to be greater in subepicardial than in subendocardial regions (1,13,14), this factor does not appear to be a problem in the detection of cardiac iron by endomyocardial biopsy.

There was variation in the grade of stainable iron in

endomyocardial tissue from the six patients, and this variation was inversely related to left ventricular function. In all six cases, iron was sarcoplasmic and *not* interstitial, indicating that cardiac iron overload should be regarded as a storage disease rather than an infiltrative process. These observations confirm previous findings in a pathologic study (14) of patients with hemochromatosis.

Fibrosis was present in all endomyocardial biopsy specimens from all of the study patients. However, the grade of fibrosis was minimal in five and mild in one despite severely decreased left ventricular function in four of the six patients. This observation suggests that fibrosis is not the only mechanism responsible for ventricular dysfunction in cardiac hemochromatosis.

Treatment of cardiac hemochromatosis. Cardiac dysfunction associated with iron overload may be reversed after iron removal by either chelation (10) or phlebotomy (3,5–9). Because cardiac hemochromatosis is a potentially reversible disorder that may mimic idiopathic dilated or restrictive cardiomyopathy, it is recommended that endomyocardial biopsy tissue from patients with unexplained heart failure be stained for iron. In two of our six cases, the diagnosis was made by endomyocardial biopsy before clinical suspicion of the disorder.

In patients with established cardiac hemochromatosis, serial endomyocardial biopsies may be indicated to document depletion of myocardial iron (12). In this regard, it is of interest that in their case report Short et al. (2) demonstrated persistence of myocardial iron on serial endomyocardial biopsies despite hypoferremia and microcytic anemia. Only after 6 years of monthly phlebotomy was iron completely absent from myocardial biopsy tissue. Therefore, in patients in whom periodic phlebotomy is not associated with a return to normal left ventricular function, serial endomyocardial biopsy should be considered to ensure that therapy has produced depletion of myocardial iron.

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