

## Cardiomyopathy Associated With Celiac Disease

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Celiac disease or celiac sprue is predominantly a disease of the small intestine characterized by chronic malabsorption in genetically susceptible individuals who ingest grains containing gluten, such as wheat, barley, and rye. Although previously believed to be uncommon, celiac disease may be present in up to 1% of the general population. Celiac disease is associated frequently with iron deficiency anemia, dermatitis herpetiformis, selective IgA deficiency, thyroid disorders, diabetes mellitus, and various connective tissue disorders but is rarely associated with cardiomyopathy. We describe a patient with celiac disease associated with cardiomyopathy whose cardiac function improved substantially after treatment with a gluten-free diet. Cardiomyopathy associated with celiac disease is a serious and potentially lethal condition. However, with early diagnosis and treatment with a gluten-free diet, cardiomyopathy in patients with celiac disease may be completely reversible.

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Celiac disease or celiac sprue is characterized by chronic malabsorption in susceptible individuals who ingest grains containing gluten, such as wheat, barley, and rye. Until recently, celiac disease was believed to be relatively uncommon. However, a recent report from Finland estimates its prevalence at 1% in the general population.<sup>1</sup> Celiac disease is associated frequently with iron deficiency anemia, dermatitis herpetiformis, selective IgA deficiency,<sup>2</sup> thyroid disorders,<sup>3</sup> diabetes mellitus,<sup>4,5</sup> and various connective tissue disorders.<sup>6-8</sup> Cardiomyopathy associated with celiac disease is reported infrequently. We describe a case of cardiomyopathy in a patient with celiac disease who had neither gastrointestinal symptoms nor manifestations of malabsorption and whose cardiac function improved substantially after treatment with a gluten-free diet.

### REPORT OF A CASE

A 70-year-old man with chronic atrial fibrillation and left ventricular dysfunction presumed to be secondary to coronary artery disease was evaluated for 4 episodes of intermittent, nonexertional chest pain during the previous 3 months, each episode lasting approximately 5 minutes. He had no associated symptoms of dyspnea, diaphoresis, or

palpitations. Dermatitis herpetiformis had been diagnosed 20 years previously; a gluten-free diet was advised, and dapsone was prescribed. The patient continued to take dapsone but for the previous 10 years had been noncompliant with a gluten-free diet. The patient had history of alcohol use, diarrhea, weight loss, or fever but had experienced drenching night sweats for approximately 4 years.

Results of physical examination revealed a blood pressure of 130/80 mm Hg and a heart rate of 100 beats/min. Cardiac rhythm was irregular with a 1/6 holosystolic murmur audible at the apex. An erythematous, papulovesicular rash was noted on the buttocks bilaterally, consistent with dermatitis herpetiformis. Findings were normal for the rest of the physical examination and for complete blood cell counts, serum chemistries, serum ferritin level, and thyroid function tests. Chest radiography revealed cardiomegaly, and echocardiography showed global hypokinesis with a left ventricular ejection fraction of 45%. Coronary angiography revealed minimal coronary atherosclerosis. Abdominal fat pad aspirate was negative for amyloid deposition. Tissue transglutaminase antibody was positive at 256 U (reference range, <20 U). Upper gastrointestinal endoscopy revealed scalloped duodenal folds, and results of a histopathologic examination revealed partial villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes. Computed tomography of the abdomen was unremarkable except for nonspecific lymphadenopathy in the porta hepatis.

Celiac disease with probable celiac disease-associated cardiomyopathy was diagnosed, and a strict gluten-free diet was initiated. The patient had been taking losartan before the diagnosis of celiac disease-associated cardiomyopathy and continued to take this drug. On evaluation 10 months later, the patient had gained 8.6 kg, the night sweats had resolved, and there were no further episodes of chest pain. The abdominal lymphadenopathy had regressed, and transthoracic echocardiography showed an ejection fraction of 65% with no wall motion abnormalities.

### DISCUSSION

Celiac disease is predominantly a disease of the small intestine that develops in genetically susceptible individuals after dietary exposure to grains containing gluten. Ingestion of gluten results in inflammation of the intestinal mucosa along with hyperplasia of the crypts and atrophy of

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TABLE 1. Literature Review (1966-2003) of Celiac Disease-Associated Cardiomyopathy\*

Reference	Patient age (y)/sex	Clinical presentation	Diagnosis	Treatment	Outcome†
Makhdoom & Randall, <sup>11</sup> 2000	49/F	CHF (EF 30%); anemia	Dilated cardiomyopathy	Gluten-free diet	EF 65%
Chuaqui et al, <sup>12</sup> 1986	34/M	CHF; diarrhea, weight loss	Dilated cardiomyopathy	Gluten-free diet	Died
Curione, <sup>13</sup> 2002	40/M	CHF (EF 38%); diarrhea, anemia	Dilated cardiomyopathy	Gluten-free diet	EF 42%
	32/M	CHF (EF 25%); diarrhea, anemia	Dilated cardiomyopathy	Gluten-free diet	EF 30%
	26/M	CHF (EF 36%); diarrhea, anemia	Dilated cardiomyopathy	Gluten-free diet‡	EF 30%
Frustaci et al, <sup>14</sup> 2002	14/F	VA (LC III); anemia	Lymphocytic myocarditis	Gluten-free diet	LC I
	36/M	CHF (EF 27%); anemia	Lymphocytic myocarditis	Gluten-free diet and immunosuppression	EF 48%
	16/F	CHF (EF 36%); anemia	Lymphocytic myocarditis	Gluten-free diet and immunosuppression	EF 54%
	38/F	VA (LC IVa); anemia	Lymphocytic myocarditis	Gluten-free diet	LC I
	32/M	CHF (EF 17%); anemia	Lymphocytic myocarditis	Gluten-free diet and immunosuppression	EF 46%
	16/F	VA (LC III); anemia	Lymphocytic myocarditis	Gluten-free diet	LC I
	35/F	VA (LC IVa); anemia	Lymphocytic myocarditis	Gluten-free diet	LC I
	22/F	CHF (EF 21%); anemia	Giant-cell myocarditis	Gluten-free diet and immunosuppression	EF 56%
	24/F	CHF (EF 32%); anemia	Lymphocytic myocarditis	Gluten-free diet and immunosuppression	EF 54%
Current study	70/M	CHF (EF 40%); dermatitis herpetiformis	Dilated cardiomyopathy	Gluten-free diet	EF 65%

\*CHF = congestive heart failure; EF = ejection fraction; LC = Low class; VA = ventricular arrhythmia.

†Patients with improved cardiac parameters also had improvement in their anemia and gastrointestinal symptoms.

‡Patient was noncompliant with the prescribed diet.

the villi of the small intestine. The inflammatory response is believed to be mediated by immune mechanisms. The classic symptom of the disease is malabsorption manifesting as diarrhea, iron deficiency anemia, and weight loss. Other manifestations include osteomalacia, coagulopathy, and peripheral neuropathy. A gluten-free diet usually results in complete resolution of the symptoms and correction of the metabolic abnormalities.

An association between celiac disease and cardiomyopathy was reported recently. One study of 52 patients reported an increased prevalence of celiac disease (5.8%) in patients with dilated cardiomyopathy.<sup>9</sup> In another study, Prati et al<sup>10</sup> found that the prevalence of celiac disease in patients with dilated cardiomyopathy was 2.2% compared with 0.35% in controls.

On review of English literature published since 1966, we found only 14 other cases of cardiomyopathy associated with celiac disease (Table 1<sup>11-14</sup>). Only patients who had both serologic evidence and biopsy findings consistent with celiac disease were included in this review. Of the 15 patients reviewed, including our patient, only 4 (27%) had a history of typical gastrointestinal symptoms of celiac

sprue.<sup>12,13</sup> Iron deficiency anemia, the most common manifestation of celiac disease in these patients, was present in 11 patients (73%).<sup>11,13,14</sup> Our patient had no gastrointestinal symptoms or iron deficiency anemia. Eleven patients (73%) presented with congestive heart failure,<sup>11-14</sup> and 4 (27%) presented with ventricular arrhythmias with normal ejection fraction.<sup>14</sup> Nine patients (60%) had biopsy-proven myocarditis,<sup>14</sup> whereas the remaining 6 (40%) were diagnosed as having dilated cardiomyopathy.<sup>11-13</sup>

Several mechanisms have been proposed for the development of cardiomyopathy in celiac sprue. Chronic malabsorption, common in celiac disease, may lead to cardiomyopathy secondary to nutritional deficiencies.<sup>15</sup> Abnormalities of intestinal permeability in patients with celiac disease may lead to increased systemic absorption of various luminal antigens or infectious agents that may cause myocardial damage through immune-mediated mechanisms.<sup>16-18</sup> Finally, myocardial injury may be secondary to an immune response directed against an antigen present in both the myocardium and the small intestine.<sup>13-15,19</sup> In our review, all 9 patients with myocarditis had detectable anti-cardiac antibodies supporting an immune-mediated mechanism.<sup>14</sup> A

recent study suggests that celiac disease is associated with cardiomyopathy rather than being a cause of cardiomyopathy because celiac disease did not cosegregate with cardiomyopathy on HLA testing.<sup>20</sup>

Of the patients reviewed, 10 (67%) were treated with a strict gluten-free diet alone.<sup>11-14</sup> The remaining 5 patients (33%) were treated with the immunosuppressive agents azathioprine and prednisone in addition to dietary restrictions.<sup>14</sup> Of the patients treated with a gluten-free diet alone, 1 patient was noncompliant and presented with worsening left ventricular function at 26-month follow-up.<sup>13</sup> Another patient died secondary to intractable heart failure 1 month after presentation.<sup>12</sup> The remaining 8 patients had substantial improvement in their ejection fraction and suppression of ventricular arrhythmias.<sup>11,13,14</sup> In 1 patient, noncompliance with a gluten-free diet 16 months after resolution of symptoms resulted in relapse of her enteropathy and cardiomyopathy with significant worsening of her ejection fraction.<sup>11</sup> All patients who were treated with a combination of immunosuppression and gluten-free diet had improvement in their left ventricular function at 12-month follow-up.<sup>14</sup>

Our case highlights several important points about celiac disease and associated conditions. Celiac disease in adults is often asymptomatic or presents with extremely few symptoms. A high degree of clinical suspicion is required to make a prompt and correct diagnosis. Cardiomyopathy associated with celiac disease is a serious and potentially lethal condition. However, if diagnosed early, cardiomyopathy may be completely reversible with initiation of a gluten-free diet. A careful medical history should be obtained to elicit gastrointestinal symptoms, and the presence of iron deficiency anemia should be investigated in patients who present with dilated cardiomyopathy or myocarditis in the absence of known etiologies. Such patients also should be screened for celiac disease with serologic tests such as tissue transglutaminase antibody.

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