Cardiomyopathy with Prominent Autophagic Degeneration, Accompanied by an Elevated Plasma Brain Natriuretic Peptide Level Despite the Lack of Overt Heart Failure

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Abstract

A 75-year-old man without overt heart failure showed an abnormally high level of brain natriuretic peptide (BNP) in plasma: 600 pg/ml. The left ventricular endomyocardial biopsy revealed prominent vacuolar degeneration in the myocytes, most of which were positive for PAS stain and BNP immunoreaction. Ultrastructurally, degenerative changes of myocytes were marked, such as deposits of glycogen and lipofuscin granules in the cytoplasm, but the most prominent finding was giant vacuoles containing degraded mitochondria, glycogen granules, myofibrils, and myelin-like structures (autophagosomes). This case may belong to one of the unclassified cardiomyopathies characterized by prominent autophagic vacuoles.
(Internal Medicine 43: 700–703, 2004)

Key words: autophagy, BNP, myocardial disease

Introduction

Autophagy is the process of sequestration of intracellular components and their subsequent degradation by lysosomal vacuoles (1). Although autophagy is ongoing as a normal process, abnormal autophagy can cause various neuromuscular degenerative diseases such as Alzheimer's disease, Parkinson's disease, and distal type myopathy (1). In a specific type of cardiomyopathy (Danon disease), cardiomyocytes include marked autophagic vacuoles in cardiac myocytes (2). In this disease, dysfunction of the autophagic process is suggested by deficiency of Lamp-2, a lysosomal protein (3, 4). Recent studies reported autophagic vacuoles in myocytes of more common heart diseases accompanied by heart failure such as dilated cardiomyopathy and aortic stenosis of the terminal stage (5–7), but the incidence of such myocytes are rare in those heart diseases and the significance is still undetermined. In this study, we examined a case of cardiomyopathy in which most of the myocytes were affected by vacuolization. In addition, this case was accompanied by a markedly elevated brain natriuretic peptide (BNP) in the plasma despite the lack of overt heart failure.

Case Report

History and clinical findings

A 75-year-old man was admitted to our hospital for examination of abnormally elevated BNP level in the plasma (529 pg/ml). He had occasionally felt chest discomfort on effort since 15 years before, although he lacked signs of heart failure. He had a history of bradycardia due to sick sinus syndrome and underwent pacemaker implantation 3 years before admission. He had no family history of cardiomyopathies. He had been temporally given a beta-blocker (Carvedilol 20 mg/day) and/or angiotensin-converting enzyme (ACE) inhibitor (Enalapril 5 mg/day) before admission, which appeared to have resulted in reduction of plasma BNP levels to some extent (Fig. 1), but the medication was withdrawn because of hypotension. On admission, he showed no symptom of myopathy. His blood pressure was relatively low (82/58 mmHg). Blood examinations repeatedly revealed significantly high levels of BNP in the plasma (211 to 814 pg/ml) with mildly high atrial natriuretic peptide (ANP, 61 to 200 pg/ml) (Fig. 1). During the clinical course, chest X-ray examination showed neither cardiomegaly nor pulmonary congestion, and his electrocardiogram at self-

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Received for publication August 11, 2003; Accepted for publication March 22, 2004
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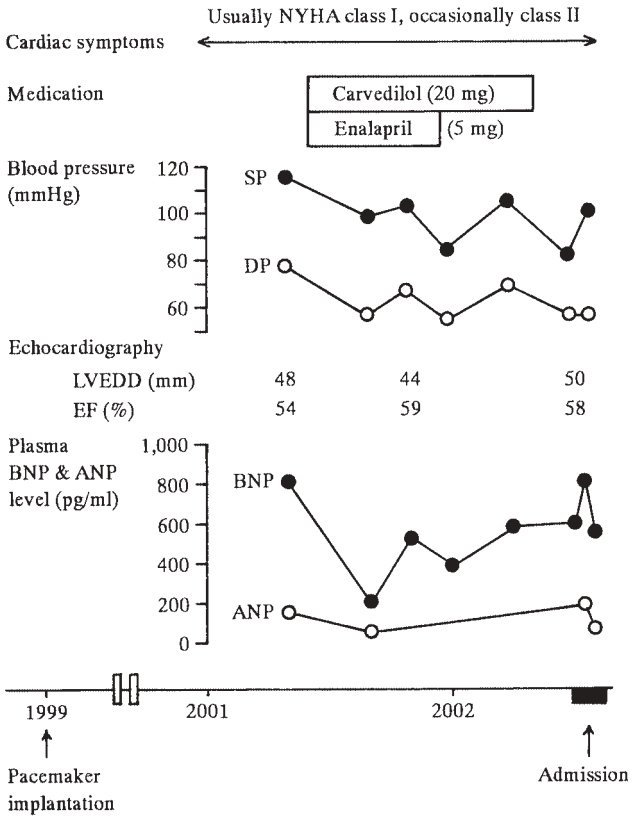

Figure 1. Clinical course and laboratory data of the patient. NYHA: New York Heart Association, SP: systolic blood pressure, DP: diastolic blood pressure, LVEDD: left ventricular end-diastolic diameter, EF: ejection fraction.

rhythm presented slightly depressed ST-T depression in V_4 to V_6 leads. The left ventricle of the heart was not dilated, but the wall motion was slightly but diffusely reduced to the lower normal level (ejection fraction =58%) by echocardiography. The echocardiography also revealed mitral regurgitation with a mild degree and left atrial dilatation. These findings were confirmed by cardiac catheterization. The cardiac index (3.9 *l*/m^2) and pulmonary artery wedge pressure (7 mmHg) were normal, thus being hemodynamically categorized into Forrester's subset I. Also, he appeared to have no apparent diastolic dysfunction of the left ventricle as evidenced by normal left ventricular end-diastolic pressure (4 mmHg) and E/A ratio of 0.8 in the echocardiographic examination, a reasonable value for his age. The coronary arteries showed no significant stenosis. Endomyocardial biopsy was performed from the left ventricle. The specimens were fixed with 10% buffered formalin and embedded in paraffin for light microscopy and immunohistochemistry or 2.5% glutaraldehyde followed by post-fixation with 1% osmium tetroxide for electron microscopy. Immunohistochemistry for BNP and ANP was performed on 4-μm thick deparaffinized sections by a previously reported method (8).

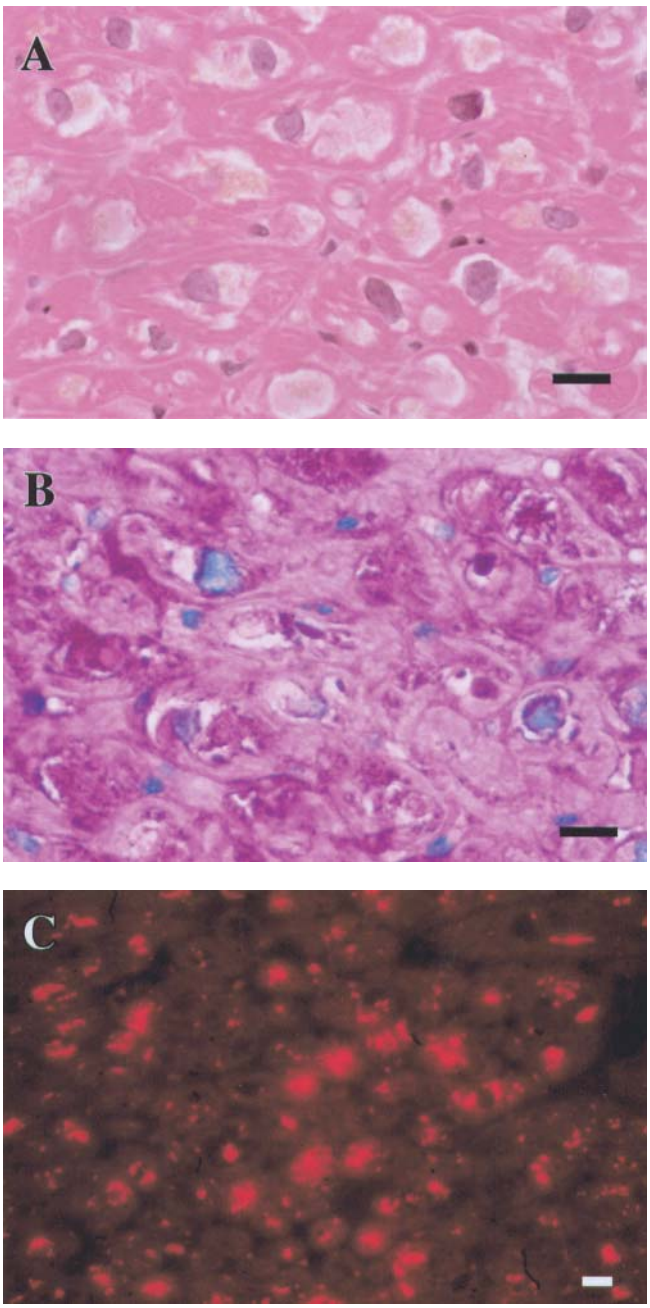

Figure 2. Histology and immunohistochemistry for BNP of the endomyocardial biopsy specimen. (A) HE stain. Myocytes are markedly vacuolated. (B) PAS stain. Most myocytes are positive for PAS. (C) BNP immunostain. BNP immunofluorescence (red) is positive in most myocytes. Bars, 10 μm.

Pathologic findings

In preparations stained with hematoxylin-eosin, most myocytes showed marked vacuolization in the cytoplasm (Fig. 2A). The size of myocytes varied, but the mean size (transverse diameter) of myocytes was slightly hypertrophic (18.3±2.9 μm). The myocytes were positive for PAS staining (Fig. 2B). Both BNP (Fig. 2C) and ANP (data not shown)

were immunohistochemically positive for most myocytes. Interstitial fibrosis was not observed.

Under an electron microscope, myocytes contained marked deposits of glycogen and lipofuscin granules mainly around the nuclei (Fig. 3A). Large vacuoles were also frequently found (Fig. 3B). The vacuoles were surrounded by one layer of membrane, consistent with lysosomes. These included degraded mitochondria, glycogen granules, myofibrils, and myelin-like membranous structures (Figs. 3C and 3D). Atrial specific granules were not found in myocytes.

Discussion

Autophagic vacuolar cardiomyopathy

Electron microscopy revealed marked deposits of glycogen and lipofuscin granules, which are commonly seen as degenerative changes in myocytes of hypertrophic and/or failing human hearts (9, 10). However, the most conspicuous finding was the large vacuoles in the cytoplasm, whose structure was consistent with giant lysosomes. The vacuoles included degraded mitochondria, glycogen, and myelin-like structures, and thus were considered autophagic vacuoles. Marked vacuoles in myocytes at the light microscopic level were considered combined features of glycogen and lipofuscin deposits and large autophagosomes.

Although glycogen deposits were marked in myocytes, glycogen storage diseases like Pompe's disease were clinically and histologically ruled out (11). Recent studies revealed autophagic vacuoles in the myocytes of hearts with dilated cardiomyopathy and in those of hearts with severe aortic stenosis, and suggested that autophagic death of myocytes might contribute to the progression of the diseases (5–7). However, the present case does not fit these disease entities because of the lack of either overt heart failure or aortic valvular disease. This case was not categorized into Danon disease, a representative autophagic vacuolar myopathy, due to the lack of skeletal myopathy and mental retardation (3). Therefore, the present cardiomyopathy is suggested as one of the unclassified cardiomyopathies. The cardiac function was only slightly impaired although the patient was elderly. Thus, the prognosis of this cardiomyopathy appears relatively good.

Increased BNP level

In general, the plasma BNP level increases in parallel with the severity of heart failure (12). However, such a high level of the plasma BNP cannot be explained by the hemodynamics in the present case. Diastolic dysfunction was also not apparent in this patient, which accelerates the increase in the plasma level of BNP (8). However, since temporal use of a beta-blocker and/or ACE inhibitor appeared to have affected the plasma BNP level, latent hemodynamic overload in this patient might also have contributed to the increase of the level to some extent. Although artificial pacing can increase the plasma BNP level (13), the level is less than 100 pg/ml, far smaller than that of the present case. We previously

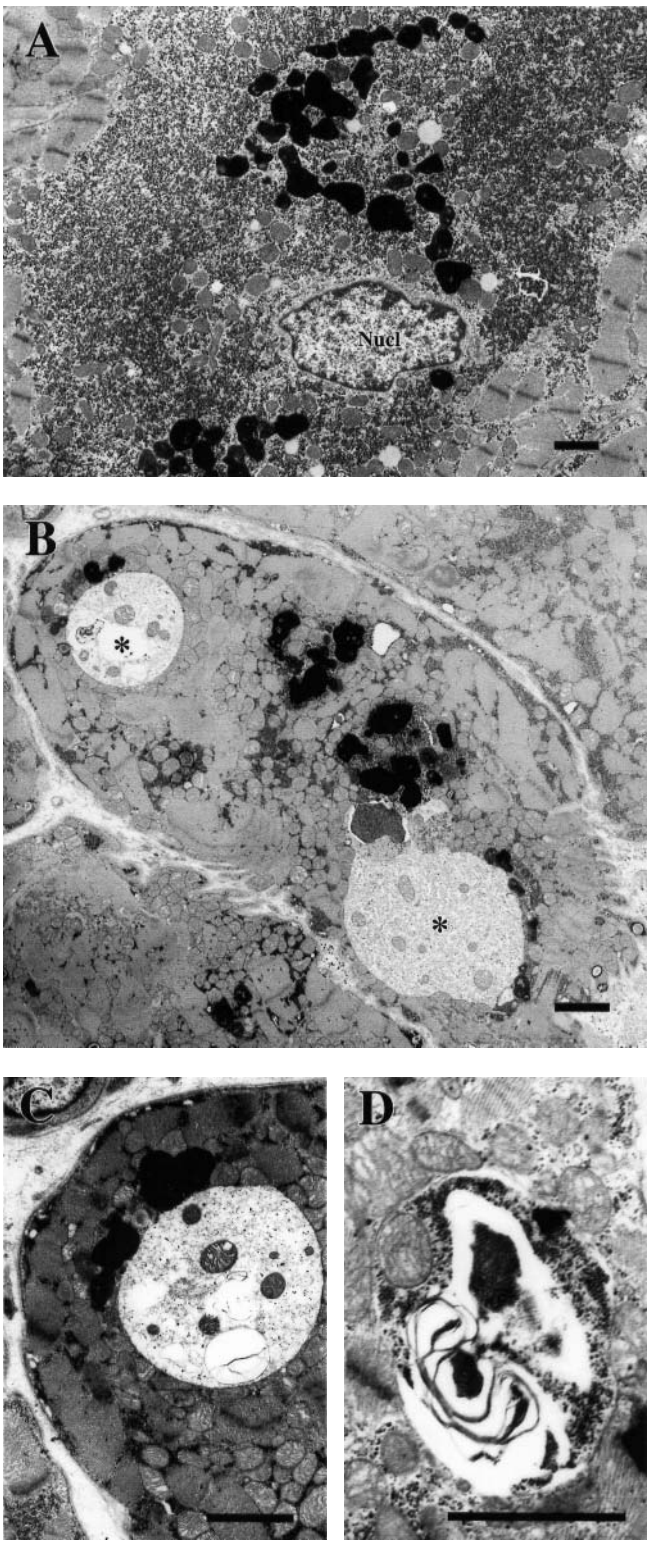

Figure 3. Electron photomicrographs of the endomyocardial biopsy specimen. (A) Deposit of glycogen and lipofuscin granules is marked around the nucleus (Nucl). (B) Giant autophagosomes (asterisks) are observed in the myocyte. (C and D) Strongly magnified views of autophagosomes containing degraded mitochondria, glycogen granules, myofibrils, and myelin-like structures. Bars, 1 μm.

reported increased BNP levels in the plasma and cardiac tissue of hearts with hypertrophic cardiomyopathy (8) and amyloid hearts (14) without systolic dysfunction. Focal stress towards individual myocytes can be a trigger for synthesis of natriuretic peptides (15). Myocytes containing space-occupying large vacuoles are assumed to render stress to the cells from inside. Thus, we suggest such an internal stress might be triggering BNP synthesis. Although we detected immunohistochemical BNP in myocytes, we could not find specific granules in myocytes under electron microscopy. Speculatively, this discrepancy might be due to BNP secretion via a constitutive pathway, without being stored in the specific granules (16). In conclusion, a case of unclassified cardiomyopathy containing prominent autophagic vacuoles in the myocytes was reported, with an increased plasma BNP level in the plasma and cardiac myocytes despite the lack of overt heart failure.

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