Atrophic Nerve Fibers in Regions of Reduced MIBG Uptake in Doxorubicin Cardiomyopathy

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A myocardial MIBG-SPECT examination was conducted 2 wk after doxorubicin chemotherapy on a 52-yr-old woman without cardiac symptoms. Despite normal ^{201}Tl scintigraphy, reduced MIBG uptake was detected in the apical anterior, inferior and lateral segments of the left ventricle. The patient died of congestive heart failure due to doxorubicin-induced cardiomyopathy 10 mo later. At necropsy, the left ventricle was markedly dilated and the apical anterior, inferior and lateral walls were thin, stiff and whitish. Nerve fibers in the apical inferior wall were atrophic and markedly fibrotic where MIBG uptake was most reduced. Nerve fibers in the septum were normal where MIBG uptake had remained normal. The histologic findings correspond with the findings on the MIBG image. MIBG imaging may detect cardiac sympathetic denervation in doxorubicin-induced cardiomyopathy before cardiac symptoms are manifest and cardiac function deteriorates.

Key Words: doxorubicin cardiomyopathy; iodine-123-MIBG; nerve fiber; single-photon emission computed tomography

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In doxorubicin-induced cardiomyopathy of rats, myocardial sympathetic dysinnervation is detected with [^{123}I-]metaiodobenzylguanidine (MIBG) prior to decreased left ventricular ejection fraction (LVEF) detected with radionuclide angiography (*1–3*). There are no reports that MIBG scintigraphy has been compared to histologic changes in myocardial nerves. We describe such findings in a woman who died 10 mo after doxorubicin-induced cardiomyopathy.

METHODS

MIBG SPECT was carried out 2 wk after previous chemotherapy. MIBG (111 MBq) was injected intravenously and SPECT was performed 15 min (early image) and 4 hr (delayed image) after postinjection. Regional MIBG uptake in five regions of interest (ROIs) of the myocardium and mediastinum were measured and expressed as counts per pixel. Each ROI was located in the anterior, septal, inferior and lateral segments of the left ventricle and mediastinum. By using the ROIs to evaluate the early and delayed images, global and regional heart-to-mediastinum ratios were determined (hG/M, hA/M, hS/M, hI/M and hL/M, in which G = global, A = anterior, S = septal; I = inferior, L = lateral). Moreover, in the early and delayed images, the global and regional washout rates of MIBG (WRG, WRA, WRS, WRI and WRL) were determined.

CASE REPORT

A 52-yr-old woman received 530 mg 320 (mg/m$_2$) doxorubicin for malignant lymphoma. She had no cardiac symptoms at that point and EF was 52% by echocardiography. Thallium-201 scintigraphy was also normal. Reduced MIBG uptake was detected in the apical anterior, inferior and lateral segments of the left ventricle (Fig. 1). Global/mediastinum activity and washout rates in early and delayed images were 1.35%, 1.12% and 49.5%, respectively. The hG/M was less than those of normal subjects (4.90 ± 1.00, mean ± s.d.) and the WRG was higher (16.5% ± 9.0%). Regional hA/M; hS/M; hI/M and hL/M in the early and delayed images were 1.20, 1.02; 1.63, 1.38; 1.18, 0.94; 1.37, 1.13, respectively, and WRA, WRS, WRI and WRL were 50.0, 48.5, 50.0 and 49.6%, respectively. The hI/M was markedly reduced. WRS was as high as other WR, although hS/M remained normal. Dyspnea and orthopnea appeared 3 mo later. At this time, the cardiac index was 2.2 liters/min/m^2, mean pulmonary capillary wedge pressure 22/mmHg by right side catheterization and the EF was 28% according to left ventriculography. The patient died 10 mo later of congestive heart failure secondary to doxorubicin-induced cardiomyopathy.

At necropsy, the left ventricle was markedly dilated and the apical, inferior and lateral walls were thin, stiff and whitish. Nerve fibers in the inferior wall were very atrophic and markedly fibrotic where MIBG uptake was most reduced (Fig. 2A, B). Conversely, nerve fibers in the septum were normal where MIBG uptake could remain normal (Fig. 2C). Moreover, atrophic myocyte and remarkable interstitial fibrosis were present in the inferior wall (Fig. 2D), although these findings were not observed in the septum (Fig. 2E).

DISCUSSION

This patient had low MIBG uptake and high washout rates in myocardial regions which later were shown to undergo dilated cardiomyopathy. It is unknown whether the atrophic and fibrotic nerve fibers are sympathetic or parasympathetic. The degree of reduced MIBG uptake may not completely correspond to that of histologic changes but necropsy was performed 10 mo after MIBG scintigraphy. Regions with reduced MIBG uptake, in which atrophic and

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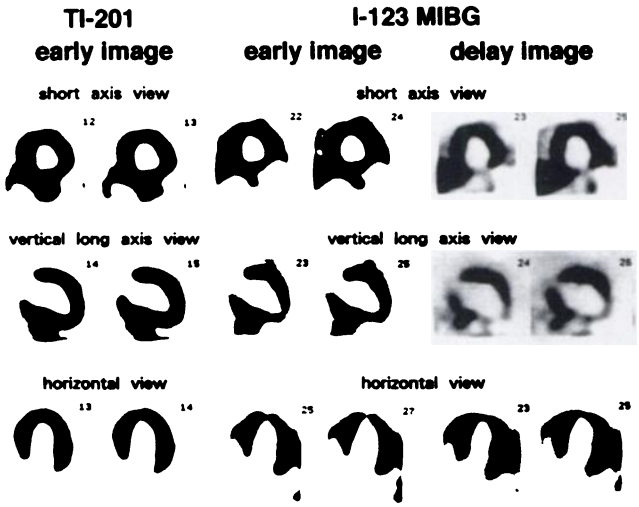

FIGURE 1. MIBG scintigraphy was performed 2 wk after the last chemotherapy treatment. The patient had no cardiac symptom and 52% LVEF was obtained by echocardiography. MIBG uptake was markedly reduced in the apical anterior, inferior and lateral walls of the left ventricle despite normal ^{201}Tl uptake.

fibrotic nerve fibers were subsequently detected, were demonstrated before the onset of cardiac symptoms as well as decreases in EF or a myocardial perfusion defect were demonstrated. These findings suggest that the damage to myocardial sympathetic nerves precedes that of myocytes and may lead to deteriorated LV function. Moreover, it is possible that neurons tend to disintegrate with doxorubicin because of interference with RNA synthesis. Neurons are dependent on RNA for normal functioning (*2*). MIBG may detect doxorubicin cardiomyopathy earlier than other noninvasive methods and may be the preferred method to determine whether doxorubicin is continued or discontinued (*4,5*).

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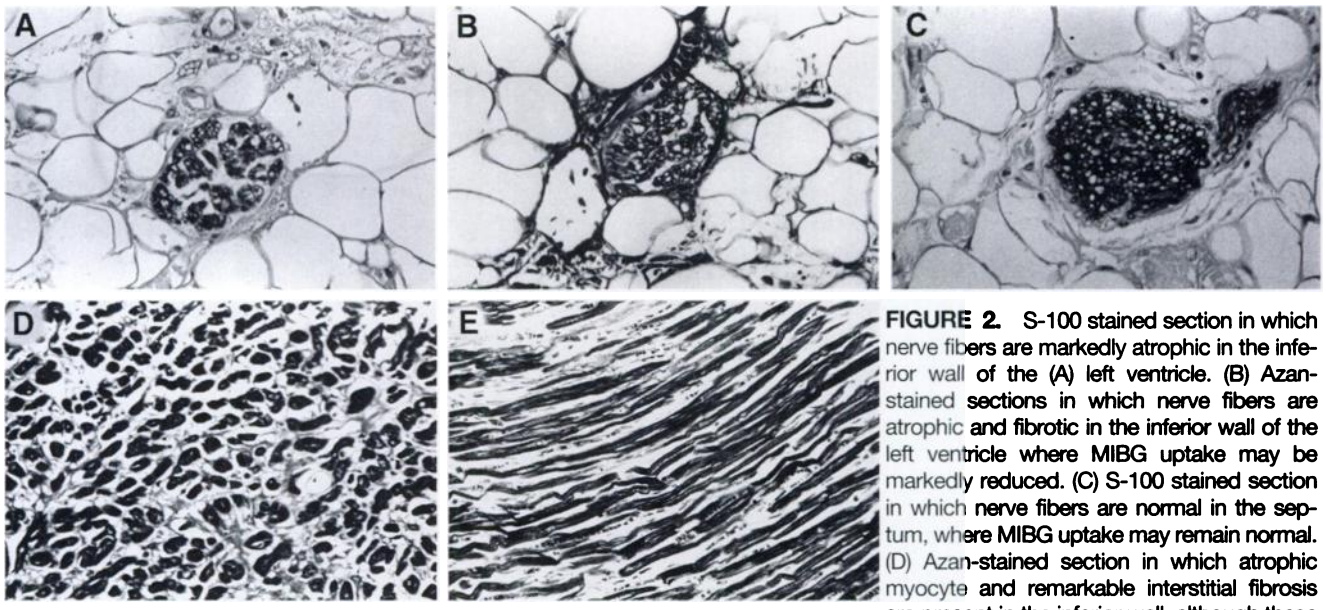

FIGURE 2. S-100 stained section in which nerve fibers are markedly atrophic in the inferior wall of the (A) left ventricle. (B) Azan-stained sections in which nerve fibers are atrophic and fibrotic in the inferior wall of the left ventricle where MIBG uptake may be markedly reduced. (C) S-100 stained section in which nerve fibers are normal in the septum, where MIBG uptake may remain normal. (D) Azan-stained section in which atrophic myocyte and remarkable interstitial fibrosis are present in the inferior wall, although these findings are not remarkable in the septum (E).