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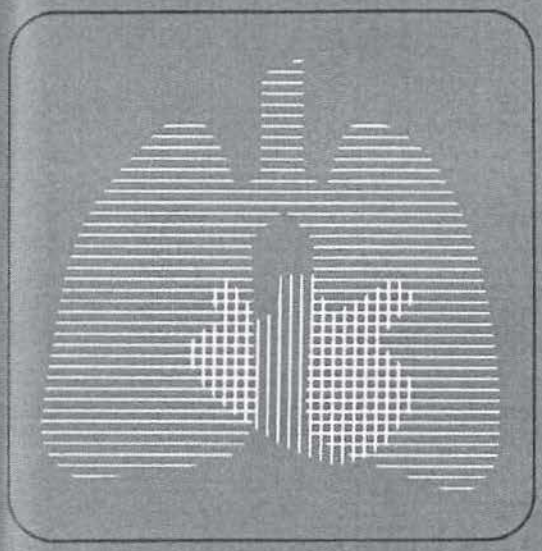

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intercostal artery.[9]

Massive hemoptysis has been controlled by surgical ligation of bronchial arteries without pulmonary resection in a few reported instances.[6-8]

To avoid complications, the catheter should be advanced selectively into the bleeding vessel and Gelfoam particles injected very slowly in order to prevent inadvertent embolization of other organs. The presence of a major spinal artery is an absolute contraindication for an embolization procedure.[6]

In the largest reported series, successful control of hemoptysis by embolization procedure without relapse within two months was achieved in approximately 90 percent of patients with the exception of those with aspergilloma.

The possibility of controlling hemoptysis by bronchial artery ligation with the aid of preoperative arteriograms may be worth consideration, especially in the patient with advanced pulmonary insufficiency who is incapable of tolerating pulmonary resection.

The bronchial circulation becomes hyperplastic with an inflammatory process in the lungs and subsides to a normal state when the process is brought under control.[6] Whether interruption of a hyperplastic circulation alters the course of an inflammatory process or the milieu for growth of tuberculosis organisms is a matter of speculation. In our case 1 and in two other cases of tuberculosis in the literature,[5,10] the course of the patients following interruption of the bronchial circulation was one of rapid recovery.

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Late, Late Doxorubicin Cardiotoxicity*

Stephen L. Gottlieb, M.D.; W. Allan Edmiston, Jr., M.D.; and L. Julian Haywood, M.D.

Cardiac toxicity is a major complication which limits the use of adriamycin as a chemotherapeutic agent. Cardiomyopathy is frequent when the total dose exceeds 600 mg/m² and occurs within one to six months after cessation of therapy. A patient is reported who developed progressive cardiomyopathy two and one-half years after receiving 580 mg/m² which apparently represents late, late cardiotoxicity.

Cardiac toxicity has been the major factor limiting the use of doxorubicin hydrochloride (Adriamycin) as an effective antineoplastic agent.[1] Cardiovascular effects of doxorubicin are manifested by acute, transient and usually benign arrhythmias and by a late dose-dependent cardiomyopathy.[2] The incidence of cardiomyopathy is greater than 30 percent among patients who receive a total dose of more than 600 mg/sq m and usually occurs within one to six months after completion of therapy.[3,4] In this report, we describe a patient with progressive heart failure 2½ years following completion of doxorubicin chemotherapy. We believe this represents a case of late, late doxorubicin cardiotoxicity.

Case Report

A 48-year-old white woman was hospitalized for progressive biventricular failure and eventually died from the severe low output state. Breast cancer had been diagnosed 16 years previously, and she was treated with surgery and nonmediastinal radiotherapy. Recurrence two years later was treated with excision, local radiation, and oophorectomy. A right axillary ulcer was noted ten years later, and chemotherapy, consisting of a six-month course of cyclophosphamide (Cytoxan), methotrexate, and 5-fluorouracil, was given. Because of bone metastasis, doxorubicin alone was then given at three-week intervals for six months. A total dose of 580 mg/sq m was given. Upon completion of doxorubicin therapy, an infusion of 30 mg/kg/day of 5-fluorouracil was given for five days at monthly intervals for a total of 16 months. Finally, 400 mg of megestrol acetate (Megace) was given four times a day for eight months. The entire course of doxorubicin therapy was completed three years prior to the hospitalization for congestive heart failure (Table 1). The symptoms of congestive heart failure began six months prior to the final hospitalization. Serial chest x-ray films to follow the course of her malignancy had not shown cardiomegaly until the time of onset of symptoms. The patient had not been hypertensive.

Physical examination at the time of the last admission revealed a cachectic, dyspneic, white woman with evidence of severe biventricular failure. She had blood pressure of 90/

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Table 1—*Patient's Medical History*

Date	Clinical Status	Therapy
1962	Breast cancer	Mastectomy—local RT*
1964	Chest wall recurrence	RT to axilla and ovaries
12/74	Bone metastases	Cyclophosphamide; methotrexate 1/75 to 7/75; fluorouracil
7/75	Progression of bone mets; increased carcinoembryonic antigen	Doxorubicin 7/75 to 2/76, 580 mg/sq m total dose
2/76	Clinically stable	Fluorouracil weekly (2/76 to 6/77)
6/77	Stable, no progression of disease	Megestral acetate 6/77 to 8/78
8/78	Congestive heart failure	Digitalis, diuretics
1/79	Patient died	

*RT indicates radiation therapy; mets, metastasis.

50 mm Hg, scleral icterus, marked jugular venous distention, bibasilar rales, cardiomegaly, a summation gallop, a holosystolic murmur consistent with tricuspid regurgitation, a pulsatile liver, and pretibial edema. The ECG demonstrated normal sinus rhythm, diffuse low voltage, and marked left atrial enlargement (Fig 1). Chest x-ray film demonstrated marked generalized cardiomegaly with pulmonary vascular redistribution. An echocardiogram revealed left atrial enlargement, increased mitral valve E-point septal separation, and decreased septal and posterior wall motion consistent with congestive cardiomyopathy; there was no pericardial thickening (Fig 2).

Hemodynamic investigation was performed because constrictive pericardial disease was considered a possible etiology for the patient's cardiac dysfunction. The intracardiac pressures were as follows (mmHg): RA: m 11, a = 19, v = 16; RV: 29/12; PA 27/16, m 24; LV 84/17; aorta: 89/51. The cardiac index was 2.1 L/sq m. The RA, RV, PA, and LV diastolic pressures were similar but not identical, and the pressure tracing morphologic findings were not typical of constrictive pericarditis. A right atrial angiogram revealed no evidence of wall thickening. A left ventricular angiogram revealed a markedly dilated LV with diffuse hypokinesis and an ejection fraction of 13 percent. The coronary arteries were normal. These data were interpreted as consistent with severe congestive cardiomyopathy. Despite diuretics, attempted afterload reduction, and intensive inotropic support, the patient deteriorated progressively and died from intractable biventricular failure. A post-mortem examination was refused by the family.

Discussion

The exact process by which doxorubicin produces cardiomyopathy is not clear. Histologic lesions consisting of myocyte damage with either myofibrillar depletion or vacuolar degeneration can be identified in animals and human cardiac biopsy specimens after only a few doses.[2,5] The toxicity is clearly related to total dosage, and the incidence of clinically significant cardiomyopathy has been controlled primarily by limitation of the total dose to 450 to 550 mg/sq m. Recently, several methods to monitor slowly changing cardiac function in patients receiving therapy have been reported. These include serial evaluation of R-wave amplitude changes on ECG, serial systolic time interval measurements, and echocardiographic and radionuclide methods to evaluate ventricular function.[2,6] It is postulated that these methods will identify patients in whom a cumulative dose of 450 mg/sq m may be exceeded, if there is need for continued use of the drug.

In this report, we have presented an unusual patient who developed severe cardiomyopathy 2¾ years after completion of doxorubicin chemotherapy. There had been no known cause of heart disease, prior evidence of cardiac decompensation, exposure to known toxins or

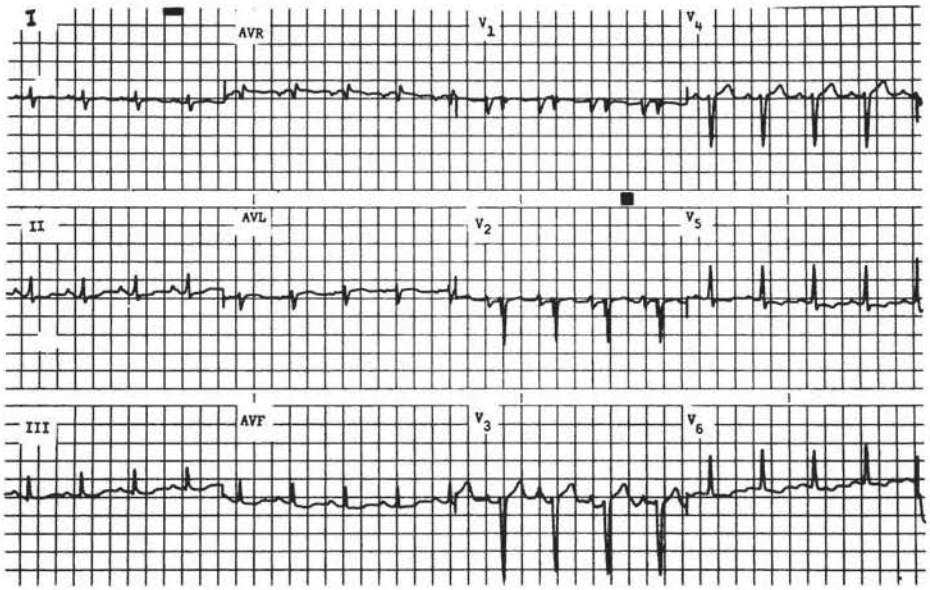

Figure 1. Twelve-lead ECG: generalized low voltage is seen with marked left atrial enlargement indicated by the large negative P-wave deflection in V_1.

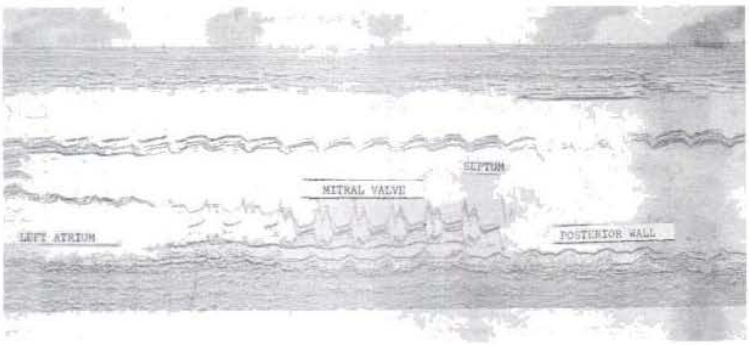

FIGURE 2. Echocardiogram: Scan from aortic root to left ventricle reveals generalized chamber dilatation and decreased wall motion.

infectious agents, or other illness likely to produce cardiac dysfunction. Furthermore, the coronary arteries were normal, and there was no evidence of pericardial thickening, constriction, or tamponade. We believe the patient's cardiac disease most likely represents what we have termed late, late doxorubicin cardiotoxicity.

This late presentation of congestive heart failure, 2½ years after completion of doxorubicin therapy, may be due to a slowly progressive cardiomyopathic process. Studies in an animal model have suggested that the doxorubicin cardiomyopathic process may be delayed and progressive.[7] However, in a large retrospective human study of patients followed for up to seven years (mean approximately 200 days), doxorubicin-induced congestive heart failure occurred at a mean of 33 days after the last dose; the range was 0 to 231 days.[8] Although we believe that doxorubicin was the major factor in the development of congestive heart failure in our patient, additional factors could have been the 5-fluorouracil or the megestral acetate which she received during the three years following the completion of the doxorubicin therapy.

Early deaths due to the malignancy and early and late cardiotoxicity limit the number of individuals who are likely to survive long enough to manifest late, late doxorubicin cardiotoxicity. Nevertheless, as current methods of treatment increase the longevity of patients with malignant disease, it is possible that more patients will develop congestive heart failure under circumstances similar to our patient. Individuals who have not manifested signs of toxicity earlier may develop such findings later in their clinical course. Long-term survivors of malignancy who have received chemotherapy with doxorubicin should be evaluated periodically to detect this potential complication.[6,8]

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Atypical Mycobacterial Lymphadenitis in an Adult*

George S. Deepe, Jr., M.D.;† Robert Capparell, M.D.;† and J. Donald Coonrod, M.D.‡

A 25-year-old woman developed lymphadenitis with *Mycobacterium avium-intracellulare*. The clinical features of the illness resembled those which have been reported in lymphadenitis with atypical mycobacteria in children. The infection was cured by resection of the infected nodes.

Lymphadenitis with atypical mycobacteria has been observed almost exclusively in children.[1,2] This report describes the clinical features of submandibular lymphadenitis caused by *Mycobacterium avium-intracellulare* in an adult.

CASE REPORT

A 25-year-old woman was referred with a two-month history of an asymptomatic right submandibular mass. There was no known exposure to tuberculosis. On physical examination a freely moveable, nontender mass measuring

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