Right heart failure after chemotherapy

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■ Cardiotoxicity associated with chemotherapeutic agents used in the treatment of cancer is well-documented. Usually this cardiotoxicity presents as a distinct syndrome in which the left ventricle is more seriously affected than the right ventricle. A case of severe right-sided ventricular dysfunction shortly after an aggressive cycle of chemotherapy for metastatic colon carcinoma is presented.
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CHEMOTHERAPEUTIC agents used in the treatment of cancer are frequently cardiotoxic.[1] Usually, the cardiotoxicity presents as a distinct entity in which the left ventricle is more seriously affected than the right. We present a case of severe right-sided dysfunction shortly after an aggressive cycle of chemotherapy for metastatic colon carcinoma. Interestingly, this patient received treatment through a hepatic artery catheter, which may have contributed to early toxicity to the right ventricle.

CASE PRESENTATION

A 49-year-old white male was transferred to our institution for further evaluation of dyspnea that had worsened over a 6-week period. He was well until September 1989, when he experienced fatigue, fever, anorexia, and melena. Diagnostic evaluation revealed a cecal mass which was later found to be adenocarcinoma. During subsequent right colectomy, cholecystectomy, and liver biopsy in October, extensive metastatic adenocarcinoma to the liver was found. On October 31, the patient began a rigorous chemotherapeutic program of vincristine sulfate, doxorubicin HCl, methotrexate, 5-fluorodeoxyuridine, mitomycin-C, interferon, 5-fluorouracil with leucovorin rescue, epoetin alfa, and carmustine. On January 25, 1990, a hepatic artery catheter was implanted for intrahepatic administration of doxorubicin, mitomycin-C, 5-fluorodeoxyuridine, and interferon, along with further courses of intravenous chemotherapy, until the last treatment on March 9, 1990. The patient received a total of 40 mg of mitomycin-C, 7500 mg of 5-fluorouracil, and 404 mg of doxorubicin (213 mg/m^2), 304 mg of which was infused directly into the hepatic artery through the indwelling catheter. He was not given any radiation therapy as part of his treatment protocol.

Onset of cardiac symptoms

The patient's cardiac symptoms began in late January 1990, with dyspnea on exertion that progressed rapidly to where he was unable to walk and was markedly dyspneic at rest. About this time he became feverish, and after a limited local workup that included a ventilation perfusion scan (which showed a low probability for pulmonary embolism), he was

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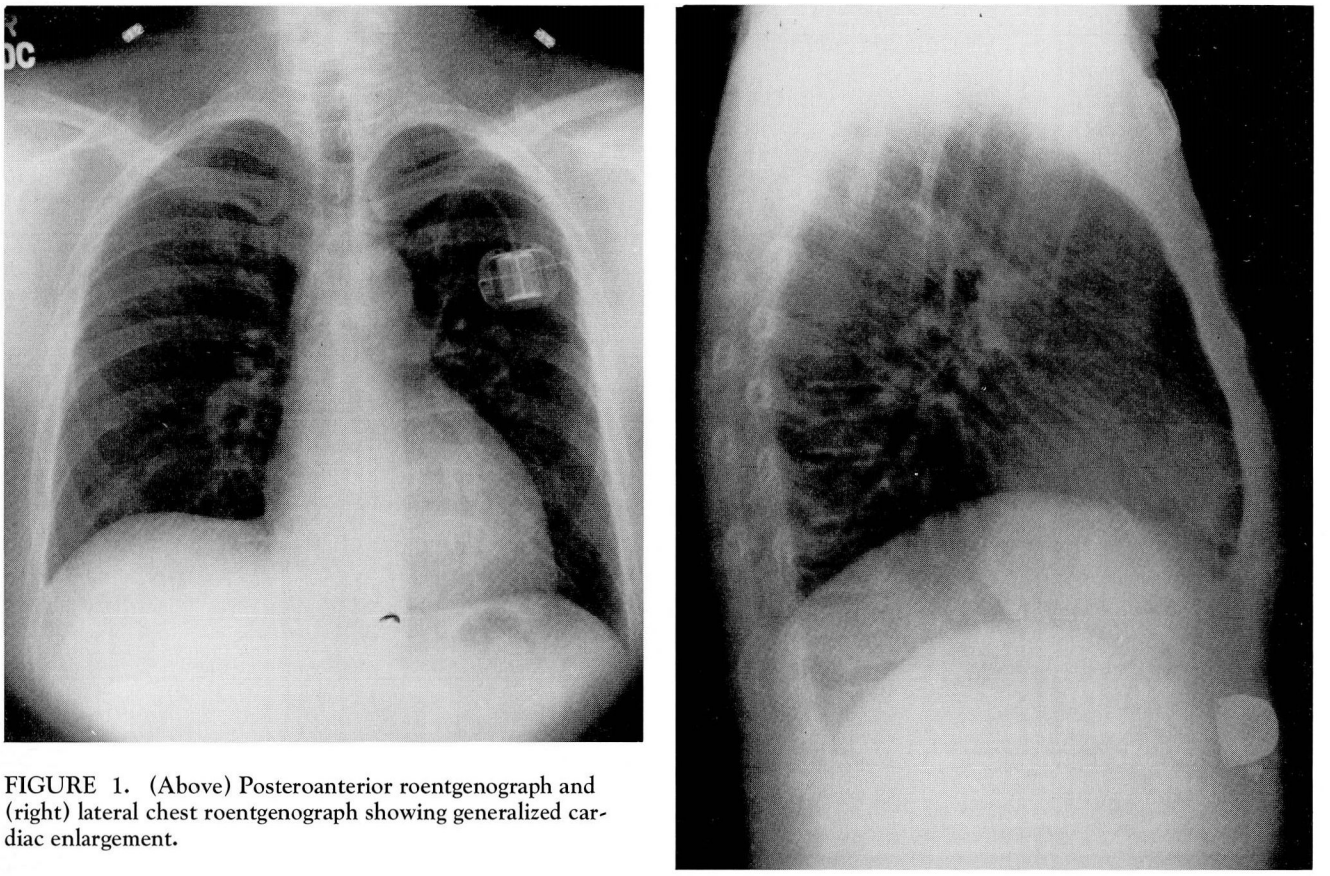

FIGURE 1. (Above) Posteroanterior roentgenograph and (right) lateral chest roentgenograph showing generalized cardiac enlargement.

treated for culture-negative endocarditis. While his fever did abate, his dyspnea did not.

The patient's history revealed alcohol abuse (10 oz per day for 20 years, none in the last 8 months) and the absence of any history of toxin exposure or cigarette smoking.

On physical examination he was cachectic with alopecia totalis, tachypneic, and mildly cyanotic on room air. He was afebrile, with a pulse of 82 beats per minute and had a blood pressure of 120/102 bilaterally. Jugular venous distension was present to the angle of the jaw at 60 degrees with prominant "v" waves. The lungs were clear and a cardiac exam revealed a regular rhythm with a normal first heart sound, a slightly increased pulmonary component of the second heart sound, and the presence of an S4 and a grade III/VI holosystolic murmur at the left sternal border and xyphoid that increased with inspiration. The liver was 10 cm below the costal margin and was mildly tender, with a palpable pulsation. An infusion catheter was noted under the skin in the right upper quadrant. Pulses were weak throughout and 2+ presacral and 1+ pretibial edema was noted.

Laboratory values on admission were as follows: serum sodium 135 mEq/L; serum potassium 4.8 mEq/L; chloride 104 mFq/L; CO_2 18.5 mEq/L; BUN 24; and creatinine 0.9 mg/dL. Lactic dehydrogenase was elevated at 533 IU, as were the serum glutamic oxaloacetic transaminase (78 IU) and the alkaline phosphatase (214 IU). The white blood cell count was 13,270 cells/mm^3 (85% neutrophils, 3% lymphocytes, 12% monocytes, 0% eosinophils); hemoglobin was 12.5 g/dL; hematocrit was 40%; and platelet count was 78,000/uL. The mean corpuscular volume was 107.3 fL, and the reticulocyte count was 5.2%. The prothrombin time and partial thromboplastin time were only slightly elevated. Urine analysis was unremarkable, except for 30 mg/dL of protein. An arterial blood gas done on room air showed a pH of 7.50, a CO_2 tension of 22 mm Hg, and O_2 tension of 49 mm Hg, with a base excess of (−)3 mEq/L, a bicarbonate of 71 mEq/L with an oxygen saturation of 89%. All cultures of the blood, urine, and sputum were negative, with no evidence of infection. Laboratory evaluation for carcinoid was negative.

Postanterior and lateral chest roentgenograms on admission were consistent with generalized cardiac enlargement. The transverse cardiac diameter was 15.5 cm and showed small bilateral pleural effusions (*Figure 1*). Electrocardiography showed normal sinus rhythm with diffuse T-wave inversion (*Figure 2*). A nuclear cardiac study with technetium Tc 99m (30 mCi) revealed a normal left ventricular ejection fraction of 70% and a severely dilated right ventricle with moderate to severe diffuse hypokinesis. Evidence of tricuspid regurgitation was present. An echocardiogram showed normal left ventricular size and function with a markedly dilated right heart, 3+ tricuspid regurgitation, and moderate pulmonary hypertension (calculated peak systolic pressure gradient of 3 meters per second by Doppler exam, corresponding to a right ventricular systolic pressure of 36 mm Hg above right atrial pressure). Pulmonary function tests indicated a moderate impairment of diffusing capacity.

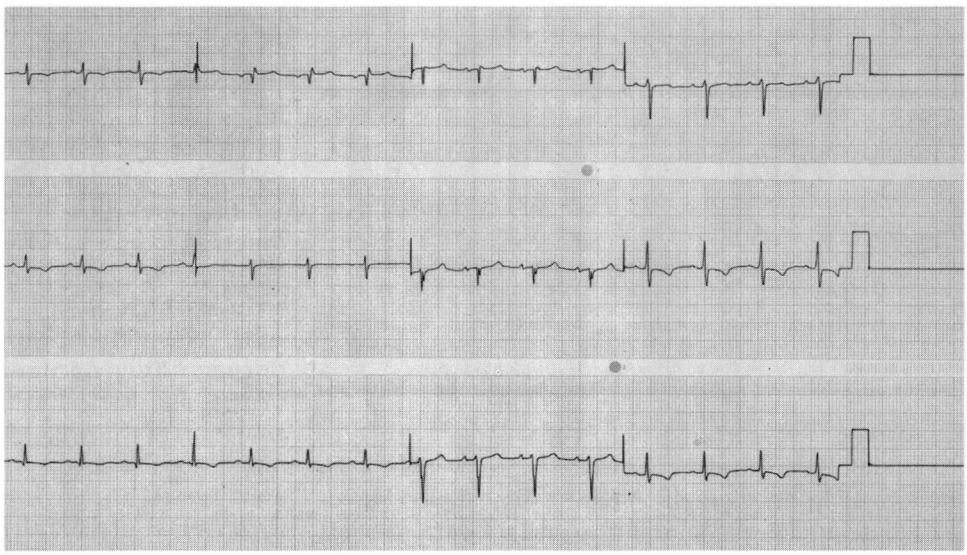

FIGURE 2. Electrocardiogram showing normal sinus rhythm with diffuse T-wave inversion.

A right and left heart catheterization was performed after platelet transfusion. His coronary arteries were normal, and the calculated left ventricular ejection fraction was 70% by left ventriculography. The right ventriculogram showed a moderately dilated chamber with global impairment of contractility. Severe tricuspid regurgitation was present, and the calculated right ventricular ejection fraction was 35%. Hemodynamics revealed a mean right atrial pressure of 10 mm Hg, a right ventricular pressure of 45/6 mm Hg, a pulmonary artery pressure of 45/25 mm Hg (mean 35), a mean wedge pressure of 6 mm Hg, a cardiac index 1.36 L/m^2, and a pulmonary vascular resistance of 12 Wood units. An arterial PO_2 was 57 mm Hg on a 3-L nasal cannula. A myocardial biopsy was performed through the right internal jugular vein using a 9-French Stanford bioptome. Five specimens were sampled from the right ventricular septum near the apex and were submitted for evaluation. The final pathology report indicated grade III doxorubicin toxicity.

The patient remained in the hospital for 7 days and was treated with digoxin, captopril, and nasal oxygen at 3 L/min with only minimal improvement in his dyspnea. At discharge, on home oxygen, he was without edema, having lost 3 kg. His final diagnosis was isolated right heart failure secondary to chemotherapy. He died within two weeks of hospital discharge. No autopsy was performed.

DISCUSSION

Doxorubicin is an anthracycline antibiotic used to treat leukemias, malignant lymphomas, and a number of solid tumors.[2] The most significant complication from doxorubicin therapy is congestive heart failure as a result of generalized impairment of myocardial contractility. The incidence of this complication is dose-related and increases significantly when the total cumulative dose is greater than 550 mg/m^2. Congestive heart failure has been reported to occur in as many as one third of patients receiving in excess of that dose.[3] Risk factors for doxorubicin cardiotoxicity include prior mediastinal irradiation, preexisting heart disease (hypertensive heart disease in particular), older age, treatment schedule, and the use of other chemotherapeutic agents.[4] The resulting cardiomyopathy usually involves the left ventricle in a diffuse process, and isolated right ventricular dysfunction is rare. Histologically, myocyte damage varies; hence, "grades" are attributed to the biopsy specimen (*Table*).[5]

TABLE
DOXORUBICIN CARDIOTOXICITY:
HISTOLOGIC CLASSIFICATION OF MYOCYTE DAMAGE

Grade 0: Normal
Grade 1: Less than 5% of the total number of cells per block are involved, with all cells exhibiting early myofibrillar loss, distended sarcoplasmic reticulum or both.
Grade 2: Groups of cells (5% to 30% of the total) with definite involvement, marked myofibrillar loss, cytoplasmic vacuolization or both.
Grade 3: Diffuse cell damage (greater than 30% of the total) the majority of cells exhibiting total loss of contractile elements and loss of organelles with mitochondrial and nuclear degeneration.[4]

Most centers have followed these patients with radionuclide angiography, systolic time intervals, or biopsy to increase the ability to detect early cardiac toxicity.[3] The amount of drug necessary to cause toxic myocardial damage appears to vary markedly. Some patients have shown evidence of doxorubicin cardiotoxicity at a total dose of 105 mg/m^2, while others have tolerated a dose of 916 mg/m^2.[3,7] This variability is not readily explained from standard risk profiles as previously outlined.[4]

Selective right ventricular failure secondary to doxorubicin is extremely rare. Sperber et al[7] reported on three patients who developed selective right ventricular failure diagnosed by radionuclide angiography. The total accumulated doses were lower than what is commonly expected to cause cardiac dysfunction (105 to 318 mg/m^2), but two of the patients received concomitant mitomycin-C chemotherapy, known to produce cardiac toxicity alone,[8] and the other received prior mediastinal irradiation.[7]

The association of possible synergy of cardiotoxic effect has previously been reported in the oncologic literature by Buzdar et al,[9] who noted that of 91 patients with advanced breast cancer who failed doxorubicin chemotherapy and subsequently received mitomycin-C, 15.3% developed congestive heart failure, compared to only 3.4% of a control group of 89 patients treated with doxorubicin without mitomycin-C.[9] Profound yet reversible global left ventricular dysfunction possibly related to 5-fluorouracil has also been reported.[10] Both of the patients in that report had received high doses of 5-fluorouracil (in addition to other chemotherapeutic agents), and both had angiographically documented resolution of their left ventricular dysfunction by the sixth day after discontinuation of the drug. Our patient had no predisposing factors for the development of congestive heart failure and, in fact, had angiographically documented normal coronary arteries and left ventricular function. He had no prior history of hypertension, and although he had a history of alcohol abuse, selective right ventricular dysfunction after heavy alcohol use has not been reported. Cases of right ventricular dysfunction caused by severe pulmonary hypertension resulting from microemboli of tumor to the pulmonary vasculature have been reported.[11]

While open lung biopsy was specifically not performed, no evidence of microemboli in this patient was found, and his cardiac biopsy confirmed doxorubicin cardiotoxicity. His extreme right ventricular dysfunction was related to the chemotherapeutic agents he received; specifically, doxorubicin, 5-fluorouracil, and mitomycin-C. Curiously, the patient received his chemotherapy directly into a hepatic artery catheter. It is unclear if this route of administration had any role in the subsequent development of right ventricular dysfunction, but intrahepatic use of these agents is a possible cause.

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