months, respectively) but contributed substantially to quality of life and were obtained with minimal morbidity.

Previous reports of vincristine-prednisone therapy for cases of monocytic leukemia are difficult to compare with the present series because of changing patterns of treatment of acute leukemia and diagnostic criteria for chronic myelomonocytic leukemia. Geary and co-workers obtained a remission of two years' duration in a symptomatic patient using combinations of cyclophosphamide, vincristine, prednisone, cytarabine, 6-mercaptopurine, thioguanine and daunorubicin hydrochloride.[7] Shaw and Nordquist[11] noted two patients with "pure" monocytic leukemia, one of whom had a "partial remission" and the other a "complete remission" while receiving vincristine and prednisone therapy alone; durations of response were not reported. In our patients, various schedules of administering vincristine and prednisone were used and optimal schedules for drug administration or inclusion of other agents remain undefined. In two patients, symptoms appeared to worsen when intervals between vincristine and prednisone cycles were extended to more than three weeks.

The effectiveness of vincristine and prednisone in a subset of patients with blast transformation of chronic myelocytic leukemia is well documented, and durations of response are similar to those noted in our patients.[12,13] Numerous studies indicate that patients with chronic myelocytic leukemia in transformation whose blast cells contain the enzyme TdT respond to vincristine and prednisone therapy, whereas those whose blasts lack this enzyme seldom respond.[11,12] We did an analysis for TdT in three patients with chronic myelomonocytic leukemia and were unable to show the enzyme in peripheral blood blasts or bone marrow from three patients responsive to the regimen of vincristine and prednisone. Obviously, conclusions regarding the predictive value of TdT in cases of chronic myelomonocytic leukemia cannot be reached using such a small number. These results suggest, however, that TdT may not predict vincristine and prednisone responsiveness in such cases. These drugs provide palliation for symptomatic patients or those with acute blastic transformation. Determining the percent of responsive patients will require larger numbers.

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Minoxidil-Associated Pericarditis and Fatal Cardiac Tamponade

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THE USE OF MINOXIDIL is associated with pericarditis.[1-3] There have been no reports in the literature of hemorrhagic pericarditis caused by minoxidil. We report this case of hemorrhagic pericardial tamponade in a patient receiving minoxidil and heparin to underscore this potential complication.

Report of a Case

The patient, a 70-year-old man with a history of severe hypertension for at least 17 years, had been admitted to hospital in 1971 and 1973 for congestive heart failure attributed to hypertension. Renal insufficiency occurred in the late 1970s with serum creatinine values between 2.5 and 3.5 mg per dl. He never required dialysis. Minoxidil was first used in December 1982 to control his hypertension. His medical regimen at the time of his final admission was furosemide, 40 mg per day; metolazone, 10 mg per day; metoprolol, 25 mg twice a day; clonidine, 0.4 mg twice a day; minoxidil, 10 mg twice a day; nifedipine, 40 mg four times a day; isosorbide dinitrate, 20 mg four times a day; potassium chloride, 40 mEq twice a day, and nitroglycerin sublingually as needed for angina.

His other medical problems included type II diabetes mellitus, hypercholesterolemia and severe diffuse atherosclerotic coronary vascular disease. He had resection of an abdominal aneurysm in February 1981. In June 1982 he had transient right arm and leg weakness for which he refused workup. In January 1983 he experienced a sensory stroke of the right side of the body from which he recovered in one month. An echocardiogram done in April 1983 showed thickened left ventricular walls and a small posterior pericardial effusion. In August 1983 he was admitted because of several hours of sharp left pleuritic chest pain. The pain radiated to the left arm but remained unchanged with different postures. There was no hemoptysis, diaphoresis or nausea.

He appeared apprehensive and in mild distress. Blood pressure was 165/88 mm of mercury with a 15 mm of mercury paradox, pulse was 108 and irregular, respiratory rate 32 and regular and temperature 36.7°C (98°F). Fine rales were present at the lung bases. On cardiac examination he had a 2/6 systolic ejection murmur but no gallop rhythm. No pleural or pericardial rub was appreciated. The jugular venous pressure was estimated at 7 cm of water. An electrocardiogram showed a new onset of atrial fibrillation with a

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ABBREVIATIONS USED IN TEXT

HLA = human leukocyte antigen
P_{CO_2} = partial carbon dioxide pressure
P_{O_2} = partial oxygen pressure

ventricular response of 110 to 120 beats per minute and more pronounced anterolateral ST-segment depression. Arterial blood gas determinations done while the patient was breathing room air showed pH 7.49, partial oxygen pressure (P_{O_2}) 58 torr and partial carbon dioxide pressure (P_{CO_2}) 29 torr (previous arterial blood gas measurements in April 1983 showed pH 7.41, P_{O_2} 90 torr and P_{CO_2} 36 torr.) A chest x-ray film showed borderline cardiomegaly and platelike atelectasis at the left lung base. A ventilation-perfusion lung scan showed good ventilation throughout both lungs and a segmental perfusion defect in the anterior basal portion of the left lower lobe.

Administration of heparin by continuous infusion was started for presumed pulmonary thromboembolism and activated partial thromboplastin times were maintained at 2.5 times control values. Warfarin therapy was initiated and the prothrombin time was 1.6 times control value at day 6 of his hospital stay. His chest pain abated gradually over three days. His cardiac rhythm converted spontaneously to normal sinus rhythm on day 1 of the hospital admission, but atrial fibrillation recurred on day 5 and intermittently thereafter until his death (two days later). On day 6 hypotension developed, which resolved with saline infusion. The hemoglobin concentration and the electrocardiogram were unchanged. On day 7 he again became hypotensive and the jugular venous pressure was estimated at 8 cm of water. A Swan-Ganz catheter was placed. Initial pressures were as follows: pulmonary wedge pressure, 15 mm of mercury; pulmonary artery diastolic pressure, 15 mm of mercury; right atrial pressure, 7 mm of mercury; cardiac output, 3.5 liters per minute. Pulmonary artery wedge tracings showed a normal X and Y descent. Saline infusion corrected his hypotension temporarily. Repeat hemodynamic measurements were as follows: pulmonary wedge pressure, 20 mm of mercury; pulmonary artery diastolic pressure, 20 mm of mercury; right atrial pressure, 15 mm of mercury; cardiac output, 1.5 liters per minute. Metabolic acidosis and obtundation developed. The Swan-Ganz catheter malfunctioned and was no longer of clinical benefit. Respiratory arrest and intractable ventricular fibrillation occurred soon afterwards and cardiopulmonary resuscitation was unsuccessful. No intracardiac injections were administered.

Postmortem findings were 100 ml of clotted and liquid blood that exited under pressure when the pericardium was incised. The pericardial sac was covered with adherent blood-tinged fibrinous exudate. Microscopically this displayed moderate lymphocytic pericardial infiltration, with a hemorrhagic fibrinous overlay (Figure 1). The 700-gram heart showed pronounced left ventricular hypertrophy and severe coronary arteriosclerosis with 80% occlusion of the anterior descending artery. On microscopic examination there were tiny areas of ischemic myocardial fiber loss without confluent areas of necrosis. Severe arteriosclerotic glomerular loss was evident throughout both kidneys. A patent distal aortic graft was identified. The remaining organs showed only the changes of acute and chronic passive hyperemia.

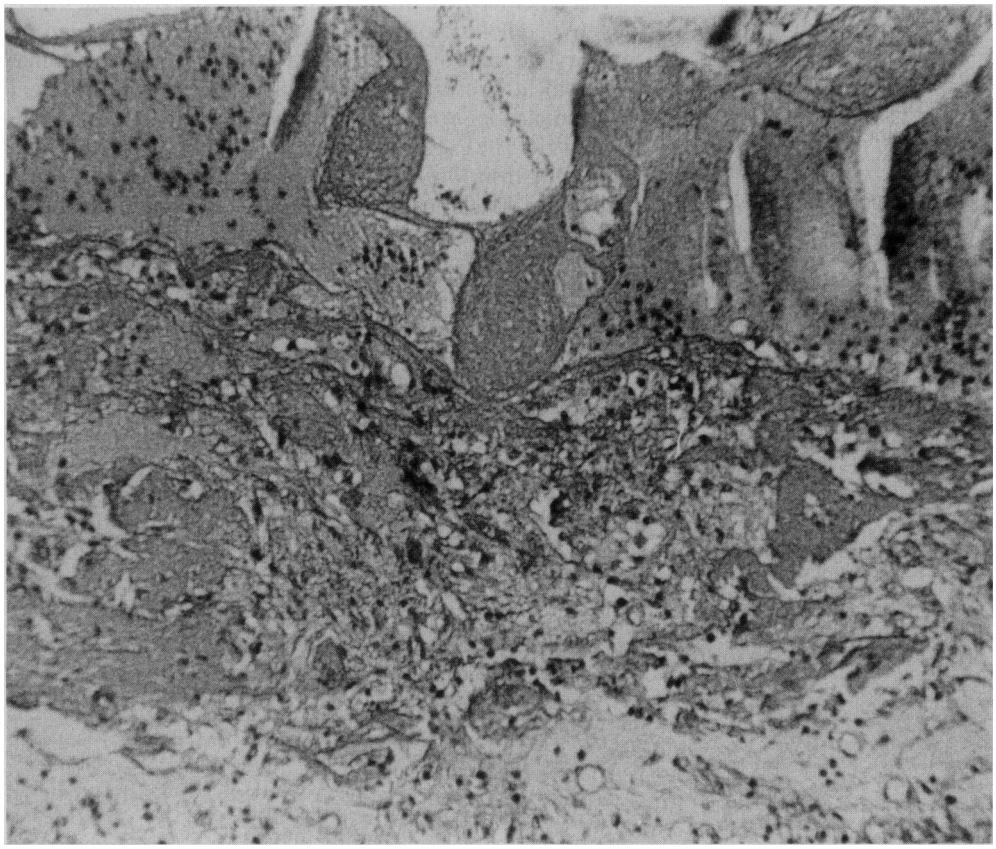

Figure 1.—Pericardium. A moderate, predominantly lymphocytic infiltrate is present within the pericardial fat as well as the overlying fibrinous exudate (hematoxylin-eosin, reduced from magnification × 350).

Discussion

The association of the use of minoxidil and pericarditis has been recognized during the past decade. Asymptomatic pericardial effusion, symptomatic pericarditis and life-threatening cardiac tamponade have all been reported with its use.[1-3] Although not all observers have agreed on this association,[4] the consensus is that minoxidil can cause pericardial disease.

A patient with renal insufficiency seems to be at particular risk for the development of minoxidil-associated pericarditis. Zarate and co-workers[1] reported an 81% prevalence of pericardial effusion in regularly dialyzed patients as contrasted with a 23% prevalence in a comparable dialysis group not treated with minoxidil. Reichgott[2] reported nine cases of pericarditis associated with minoxidil. All the patients had renal dysfunction at the time pericarditis developed (not all were receiving dialysis). Marquez-Julio and associates[2] prospectively observed that of 18 patients being treated with minoxidil for refractory hypertension, pericardial effusion developed in 7 (39%). Five of these patients had renal impairment. Our patient had renal insufficiency but never required dialysis.

The largest series in which the relation between pericardial disorders and minoxidil was examined is a retrospective review from the Upjohn Company and the University of Massachusetts.[4] The study consisted of a treatment group using open-labeled minoxidil on an experimental protocol for severe hypertension. It contained 477 dialysis patients and 1,392 nondialysis patients. The diagnosis of pericardial disorders was based on reports of adverse reactions, intercurrent medical events and deaths. This most likely underestimated the incidence of pericardial disease. In the dialysis group, 46 pericardial disorders were recognized, 14 with tamponade. The nondialysis group had 45 cases of pericardial disorders, 7 with tamponade. In the nondialysis group 4 of 32 patients with effusion alone had no recognizable risk factor; 2 of the patients with tamponade had no recognizable risk factor. The authors felt that no association was shown between minoxidil and pericarditis. Their conclusion was based on similar incidences of pericardial disease within the dialysis group and historical controls. The design of this study does not lend itself to definitive conclusions. It was also suggested that a 4.5-kg (10-lb) or greater weight gain during minoxidil therapy may be a marker for pericardial disease developing in otherwise risk-free patients. Our patient did not have any weight gain while being treated with minoxidil.

Pathologic descriptions of the features of minoxidil-related pericarditis are available from the literature. Evans and Tucker[5] reported chronic fibrinous pericarditis at autopsy. Houston and colleagues[6] and Webb and Whale[7] described exudative characteristics of a pericardial effusion at pericardiocentesis. Webb and Whale's case of pericardial effusion with a high protein content occurred in a patient with no underlying risk factor. Interestingly, the patient also had a pleural effusion. Human leukocyte antigen (HLA) typing of this patient included B8 and B27 alleles. As the authors discuss, both alleles are associated with autoimmune diseases. There is no report of an analysis of the HLA state of other patients with minoxidil-induced pericarditis. At autopsy our patient had chronic fibrinous pericarditis consistent with previous pathologic findings of minoxidil-related pericarditis.

The common causes of hemopericardium include neoplasm, myocardial and great vessel ruptures into the pericardial sac, trauma, surgical procedures and anticoagulant therapy.[8] In our patient the risk factors for hemopericardium were his anticoagulation and pericarditis. Guberman and coworkers[9] found 11 of 56 medical patients with cardiac tamponade to be anticoagulated in a retrospective review at the University of Cincinnati. Five cases occurred during anticoagulation for acute myocardial infarction and six cases in uremic patients receiving dialysis long term with intermittent anticoagulation. Of the remaining five receiving anticoagulants for various reasons, three were excessively anticoagulated at the time of tamponade. Our patient was not excessively anticoagulated. Blau and associates[10] and Goodman[11] have separately reemphasized the danger of anticoagulation with concomitant pericarditis.

In four autopsy series,[12-15] an incidence of 2% to 4% of hemopericardium associated with cardiopulmonary resuscitation has been reported. None of these series specifically analyzes the risk of hemopericardium in anticoagulated patients during cardiopulmonary resuscitation. Whereas our case might be explained as pericardial bleeding caused by cardiopulmonary resuscitation, this would recognize the pericarditis as only coincidental and ignore the terminal clinical course and hemodynamic variables consistent with but not classical for cardiac tamponade.

This case reemphasizes the difficulty of antemortem recognition of cardiac tamponade, particularly with atypical hemodynamic values, and the danger of anticoagulation in a case of pericarditis. We wish to alert clinicians to the possibility of clinically unrecognized pericarditis in a patient using minoxidil. When such a patient requires anticoagulation, we recommend careful clinical monitoring at the least or consideration of alternative antihypertensive therapy.

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