Cardiac Necrobiotic (Rheumatoid?) Granulomas Without Arthritis

Report of Two Cases

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Cardiac necrobiotic lesions resembling rheumatoid granulomas were discovered in 2 patients without evidence of arthritis. Evidence from the literature indicates that pulmonary and subcutaneous nodules may occur before arthritis or before the appearance of the rheumatoid factor, and that cardiac lesions may occur early in the course of rheumatoid disease. Even in the absence of obvious arthritis and the rheumatoid factor, rheumatoid disease should be considered part of the differential diagnosis of acquired valvular heart lesions.

Various cardiac lesions associated with rheumatoid disease include nonspecific endocarditis, myocarditis, arteritis, amyloidosis and pericarditis. However, the most specific and dramatic is the necrobiotic granuloma. Since the initial description by Baggenstoss and Rosenberg in 1941, at least 69 patients with cardiac rheumatoid granulomas have been recorded. In 1958, Cruickshank reviewed 13 such patients adding 5 from his own material. Since then, 31 patients have been briefly mentioned in the literature and 20 others described in some detail. All detailed reports have described patients with objective signs of arthritis, although the joint disease was regarded occasionally as inactive, transient and in 1 patient, probably not of the rheumatoid type. This report concerns 2 patients in whom cardiac necrobiotic lesions resembling rheumatoid granulomas were encountered in the absence of arthritis.

CASE REPORTS

Case 1. R.F.H., a 46-year-old bartender, entered the hospital Jan 25, 1962 because of swelling of his legs and dyspnea. Two months before admission he noted the insidious onset of fatigue, exertional dyspnea, ankle edema and a nonproductive cough. Dec 14, 1961 he had been admitted to another hospital with signs of severe congestive heart failure. A loud, decrescendo, diastolic murmur was heard at the left sternal border. Eight blood cultures showed no growth. Although he was never febrile, the patient was...
given a course of 8,000,000 units of penicillin intramuscularly before discharge Jan 9, 1962. Because of recurrent dyspnea and edema, he was admitted to the Ann Arbor Veterans Administration Hospital 16 days later.

The patient had no history of chest pain, hypertension, syphilis, or recent chest trauma. He had been treated at another hospital in 1957 because of peripheral neuropathy ascribed to alcoholism. There was no history of joint pain or swelling except for a traumatic hemarthrosis in 1958. The heart murmur had been detected neither during hospital admissions before 1962 nor at periodic physical examinations required by his employment. Serological tests for syphilis on these occasions and during his Army service in World War II had been uniformly negative.

Examination of a well-developed, well-nourished, dyspneic man showed BP 148/44 mm Hg, pulse 100/min and temperature 97.8° F. A precordial heave and enlargement of the left border of cardiac dullness to the anterior axillary line were noted. There was a loud, high-pitched, blowing, diastolic murmur, heard best at the base of the heart and along the left sternal border as well as a faint systolic murmur at the second interspace. The radial pulse was waterhammer in character. Marked, pitting edema involved the legs to the level of the knees. There was patchy loss of sensation to pin-prick and light touch over the lower legs. The peripheral joints were normal.

Hemoglobin, WBC count and differential, urinalysis, BUN, fasting blood sugar, serum protein, and cerebrospinal fluid protein were normal. Five blood cultures showed no growth. Two antistreptolysin O determinations were 125 and 250 Todd units respectively. The serum and cerebrospinal fluid VDRL serologic tests for syphilis were nonreactive. A chest roentgenogram indicated generalized cardiac enlargement with pulmonary vascular congestion.

The electrocardiogram revealed ST segment depression and flat T-waves in the limb leads and over the left precordium. The PR interval was 0.21 sec.

Despite diuresis he remained severely dyspneic. On Day 18 after admission, he became febrile and produced large quantities of pink-tinged sputum. Signs of bilateral pneumonitis progressed until death 12 days later. Sputum cultures grew coagulase positive Staphylococci and Pseudomonas.

Autopsy was performed about 10 hr after death. Both lungs showed congestion, edema, focal hemorrhage and extensive, acute purulent lobular pneumonia. The heart weighed 570 g. All chambers were slightly dilated but free of thrombi. Both left and right ventricular walls were hypertrophied: the left 17 mm thick, and the right, 5 mm. The circumference of the aortic valve was 98 mm and that of the mitral valve 108 mm; there was a slight thickening of both the valve rings and the aortic cusps. The pulmonary and tricuspid valves were normal. There was minimal coronary arterial and aortic atherosclerosis.

Histologic examination of the mitral and aortic valve rings revealed severe chronic inflammatory changes characterized by proliferation of granulation tissue; dense infiltration of lymphocytes, plasma cells and histiocytes; and extensive fibrosis. Both rings contained necrobiotic granulomas consisting of several areas of fibrinoid necrosis surrounded by palisaded histiocytes with a peripheral zone of lymphocytes and plasma cells (Fig 1-2).

Special stains for bacteria, acid fast bacilli, spiröchetes and fungi were negative. Pericardial fibrous adhesions with chronic inflammatory cell infiltrates were present. The myocardium exhibited hypertrophy, focal fibrosis, and focal chronic myocarditis. No Aschoff bodies were found.

The intima of the aorta contained atheromatous changes with acellular eosinophilic material and focal calcification. In many areas of the adventitia, proliferation of granulation tissue and dense infiltration by lymphocytes and plasma cells were noted, particularly, about the small vascular channels. The media showed nonspecific degenerative changes with vascularization and infiltration by lymphocytes and plasma cells. In the sinuses of Valsalva, the aortic wall was necrotic and covered by a layer of fibrin.

Case 2. M.E.P., a 37-year-old laborer, entered the hospital Nov 8, 1964 because of fever of 4 days' duration and right flank pain of 1 day's duration. There was no history of joint pain or swelling.

Examination showed a well-nourished, acutely ill man with marked tenderness in the right costovertebral angle and flank. The heart was not enlarged to percussion. A faint holosystolic murmur was heard at the apex. The WBC count was 17,500/cumm with 82% polymorphonuclear neutrophils and 18% lymphocytes. The hemoglobin, hematocrit, serum protein electrophoresis and hemoglobin electrophoresis were normal. The urine sediment showed 8-5 leukocytes and 10-20 RBC per high-power field. Urine cultures and two blood cultures done shortly after admission showed no growth.

The latex fixation test, 6 lupus erythematosus
cell preparations, a direct and indirect Coomb’s test and several antinuclear factor determinations were negative. Febrile agglutinins for S typhosa H, S typhosa O, S paratyphi A, S paratyphi B, and B abortus were negative. Two antistreptolysin O determinations were 12 and 50 Todd units respectively. The VDRL was nonreactive. A chest roentgenogram, 2 intravenous pyelograms and an electrocardiogram were normal. Intradermal skin tests were negative with tuberculin, positive with mumps antigen, and highly positive with histoplasmin. A histoplasmin complement fixation test was equivocal; 2 repeat determinations were negative.

During the first week of hospitalization, there were daily fever spikes to 103° F. The patient complained of moderate pain in the wrists, elbows and knees, although no objective joint findings were noted.

Nov 17, tenderness and rubor appeared in the left hypothenar area and small finger. Cultures taken from a splinter hemorrhage on the finger failed to show growth. A percutaneous renal biopsy and a gastrocnemius muscle biopsy were normal.
Prednisone was started Nov 24, in a daily dose of 80–120 mg for 6 days with gradual withdrawal over the following 2 weeks. This regimen produced no significant change in the fever. An exploratory laparotomy Dec 9 was unremarkable.

At this time, the systolic murmur at the apex increased in intensity. The WBC count ranged from 9,000 to 23,000/cumm. The hemoglobin decreased progressively to 7.3 g/100 ml. In spite of the numerous negative blood cultures, bacterial endocarditis was regarded as the prime diagnostic possibility. The patient received 20 million units of penicillin with 2 g streptomycin daily for 7 days and 550 mg amphotericin B for 10 days without effect upon his fever, which appeared to subside spontaneously in the ninth hospital week. At this time, the apical systolic murmur became louder and radiated to the axilla. In spite of digitalization, pulmonary edema occurred. Cardiac catheterization revealed a right ventricular pressure of 100/0-14, main pulmonary artery pressure of 105/43 (mean 43), wedge pressure at 2 different locations of 36 and 43 with large V-waves and left ventricular pressure of 144/0-10-32. These signs indicated gross
mitral insufficiency, some degree of mitral obstruction and evidence of left- and right-sided heart failure. Cardiac cineangiograms also demonstrated gross mitral insufficiency.

At open heart surgery Feb 9, 1965, granulations were found on the posterior and aortic leaflets of the mitral valve. The mitral valve was excised, and a Starr-Edwards ball valve prosthesis inserted. Grossly, the surgical specimen was a fibrotic mitral valve with attached fibrotic, shortened chordae tendineae. Along the edge of the valve and near the point of fusion, there appeared to be fibrinous material.

Histologically, there was increased vascularity with extensive collagenous scarring, throughout the valve; proliferation of granulation tissue; and infiltration by lymphocytes, plasma cells and histiocytes. A large area of fibrinoid necrosis was present in one area near the base of the valve (Fig 3). This area of necrosis was surrounded by a few palisaded histiocytes and a peripheral zone of lymphocytes and plasma cells. The papillary

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muscle exhibited early degenerative changes and a slight infiltration by chronic inflammatory cells. The pathologic diagnosis was endocarditis with "rheumatoid-like" granuloma formation.

Cultures of the excised valve and blood specimens taken from the heart by catheter were negative for bacteria and fungi. A total of 23 pre- and postoperative blood cultures were negative for microorganisms, including several cultures for tuberculosis, fungi, and anaerobic bacteria.

Postoperatively, the patient made an uneventful recovery. Several months after surgery, he had mild generalized arthralgia which lasted a few weeks and responded well to salicylates. No objective joint changes were noted. The latex fixation test was negative.

When he was examined at his home by one of us (K.L.) July 1967, his peripheral joints were found to be normal. There were no subcutaneous nodules. The patient had no morning stiffness or joint pain. A latex fixation test and FII inhibition test for rheumatoid factor were negative.

DISCUSSION

Both patients were previously healthy, middle-aged men in whom valvular lesions and intractable heart failure appeared. In the face of negative blood cultures, both were treated presumptively for bacterial endocarditis, seemingly to no avail. In neither case, was rheumatoid disease suspected prior to tissue examination.

The clinicians caring for the patients regarded the diagnoses of rheumatoid heart disease with skepticism for several reasons: (1) Such cardiac involvement without arthritis was unprecedented; (2) In Case 2, the argument for rheumatoid disease was weakened by failure to demonstrate rheumatoid factor in the blood (the test was not obtained in the fatal case); (3) Neither patient had subcutaneous nodules; nor have such nodules appeared during a 4-year follow-up of the nonfatal case.

Rheumatoid granulomas at various sites may occasionally presage arthritis. Subcutaneous nodules in adults have appeared several years before the onset of rheumatoid arthritis. Nonpneumoconiotic rheumatoid pulmonary granulomas have occurred with minimal evidence of arthritis and have preceded joint symptoms.

Various, less specific visceral manifestations have been proposed as presenting lesions of rheumatoid disease prior to the onset of arthritis, including pericarditis, complete atroventricular block, pleural effusion, Caplan's syndrome, and diffuse interstitial pulmonary fibrosis.

Rheumatoid factor is not always demonstrable in patients presenting with rheumatoid arthritis and juxta-articular nodules. The factor was not detectable in 9 of 54 such patients, including 2 patients in which biopsy confirmed the diagnosis of rheumatoid nodules. In a case of rheumatoid arthritis, tests for rheumatoid factor did not become positive until at least 5 years after the appearance of well-documented pulmonary rheumatoid granulomas. Tests for rheumatoid factor in 7 patients with established rheumatoid arthritis associated with cardiac granulomas were positive in 6 and negative in 1.

The absence of subcutaneous nodules in our patients does not weigh heavily against a diagnosis of rheumatoid disease. Subcutaneous nodules were present in 10 of 18 patients with rheumatoid cardiac granulomas reviewed by Cruickshank and in 14 of 21 later patients. In a review of 15 patients with rheumatoid pulmonary granulomas, only 4 were found to have subcutaneous nodules.

Three recently published cases of rheumatoid heart disease complement our experience. A report by Lassiter and Tassy illustrates that heart involvement may indeed be a very early, if not a presenting, manifestation of rheumatoid disease. At the initial physical examination only 2 months after onset of joint pain, their patient had...
a loud basal systolic murmur with a palpable thrill in addition to objective signs of rheumatoid arthritis. He developed progressive heart failure and died 4 years later. At postmortem examination, large rheumatoid granulomas were found in the aortic ring.

Legier described a patient who acquired aortic insufficiency at age 68 and soon died of intractable heart failure. A large rheumatoid granuloma involving the aortic valve and a smaller granuloma in the epicardium were discovered at autopsy. This patient had no evidence of arthritis except for unilateral hip disease since childhood, not at all suggestive of rheumatoid arthritis. As in our first patient, rheumatoid disease was not suspected during life, and a test for rheumatoid factor was not done.

Finally, Lefkovits, Kaplan and Young have reported a patient with minimal evidence of rheumatoid arthritis, consisting of arthralgia of 10 years' duration, transient episodes of joint swelling and an ulnar subcutaneous nodule. As in our second patient, there were periods of unexplained fever, and tests for rheumatoid factor were repeatedly negative. Fatal aortic insufficiency ensued due to rheumatoid granulomas at the base of the valve.

Since rheumatoid granulomas rarely calcify, one might speculate that undetected visceral lesions are, not uncommonly, early or even initial lesions of rheumatoid disease. Nearly a century ago, Charcot advanced the argument that inflammatory rheumatoid cardiac lesions are not rare, but merely go undetected. At autopsy of rheumatoid patients, the cardiac valve leaflets and rings frequently contain lipid and calcium deposits with attendant fibrosis, suggesting that preexisting rheumatoid disease may have been present. This interpretation is supported by the occasional end-stage pathology of rheumatoid subcutaneous nodules in which nonspecific, fibrous, solid or cystic lesions are found.

Since we failed to muster extracardiac evidence for rheumatoid arthritis in our cases, the argument for the rheumatoid etiology of the heart disease must remain inconclusive. Even chronic subcutaneous nodules over pressure points showing typical fibrinoid and palisading are not specific for rheumatoid disease. However, the location of the granulomas deep within the core of the leaflets (Case 2) and involving the rings (Case 1) is typical of necrobiotic rheumatoid lesions. Active or inactive pericarditis, though frequently patchy in distribution and clinically silent, has almost invariably been described in the reported cases of rheumatoid heart disease. Pericarditis was found in our first patient but not in our second, where no gross pericardial changes were apparent during cardiac surgery. Chordae tendineae may be involved occasionally by linear lesions extending from the typical nodular necrobiotic process in the mitral valve ring.

Because of fever and apparent embolic manifestations in Case 2, infective endocarditis could not be ruled out as a possible alternative diagnosis, despite negative histologic and cultural evidence. Reports since 1951 have failed to demonstrate bacteremia in 7–28% of cases of this disease. Admittedly, granulomas due to syphilis and tuberculosis may resemble rheumatoid nodules. These two diseases were adequately ruled out in our cases, but the possibility remains that we have overlooked another inapparent infective disease.

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REFERENCES


