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GRANULOMATOUS MYOCARDITIS

WARD M. O'DONNELL, M.D.
RICHARD H. MANN, M.D.
Lancaster, Pa.

From the Departments of Pathology and Med-
icine, Lancaster General Hospital

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Asymptomatic giant cell granulomatous myocarditis

Ward M. O'Donnell, M.D.

Richard H. Mann, M.D.

Lancaster, Pa.

Giant cell myocarditis is an uncommon postmortem finding, with only 23 cases reported in the English literature.¹ About half of the patients in whom this morphologic change was seen died suddenly and unexpectedly. The remainder followed a course of rapidly progressive, refractory congestive heart failure, associated with a high incidence of cardiac arrhythmias.

Giant cell myocarditis is a disease of unknown etiology and its differentiation from granulomatous myocarditis has been questioned.² The relationship of this form of myocarditis to the structural alteration seen in syphilis, sarcoid, tuberculosis, Fiedler's myocarditis, systemic fungus, or protozoan disease is unsettled. The extracardiac involvement seen in some cases of giant cell myocarditis, in which associated granulomas are found in the lungs and regional lymph nodes, tends to remove this disease from the realm of an isolated myocarditis. The striking observation of giant cells of either the Langhans type or of myogenic origin in the fibrous granulomatous tissue separates this morphologic entity from the more common degenerative or inflammatory lesions of the myocardium. In fact, it is unusual to have giant cell formation as part of the reparative process in any heart lesion other than in the known chronic infective granulomas.

Our interest in this problem was stimulated by a recent patient whose death was

unrelated to his cardiac function, but whose heart, at autopsy, showed the pathologic changes of giant cell granulomatous myocarditis. This patient never had symptoms which could be related to an underlying cardiac disease. The purpose of this report is to emphasize that giant cell myocarditis may exist in the absence of symptomatic heart disease; that the morphologic process may be protracted, with death occurring from intercurrent disease; that the involvement of multiple organs can occur; and that this pathologic change can be seen in the elderly as well as in the young. Finally, the histopathologic changes in the kidneys in this case lend support for a hypersensitivity etiology.

Case report

A 76-year-old man was admitted to the Lancaster General Hospital with a 10-day history of slurred speech, followed by aphasia, lack of comprehension, and finally stupor. There had been a history of typical grand mal type seizures for several years. The seizures were controlled by Dilantin. There was no history of head injury. The patient was known to have been diabetic for 5 years and was controlled by diet and Orinase.

A history was obtained of intermittent, migratory pain in the joints covering a 50-year period, and associated with episodes of red, painful, swollen joints. Movement of the knees and ankles had been limited. The clinical picture was that of gouty arthritis, and blood uric acid levels up to 10.3 mg. per cent had been recorded. The only medication used was aspirin. There was no history of exertional dyspnea, chest pain, or hypertension.

From the Departments of Pathology and Medicine, Lancaster General Hospital, Lancaster, Pa.
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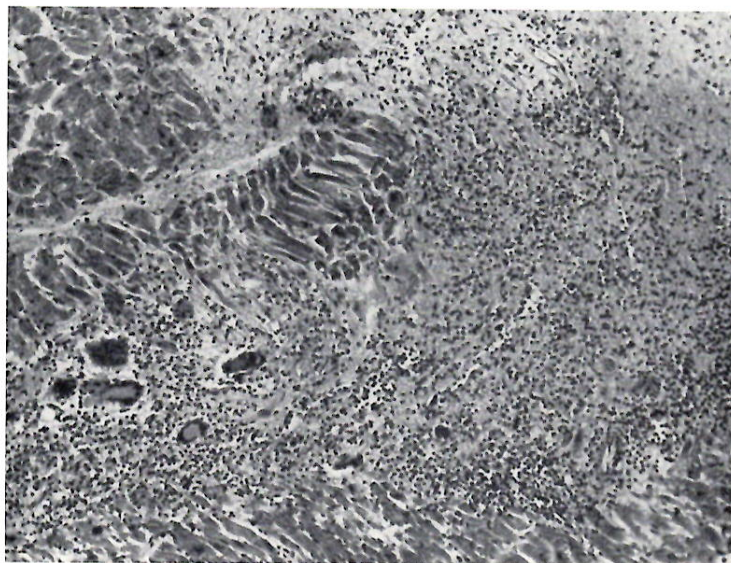


Fig. 1. Myocardium showing focal replacement by granulation tissue. The giant cells are of the Langhans and foreign body types. Magnification $\times 100$.

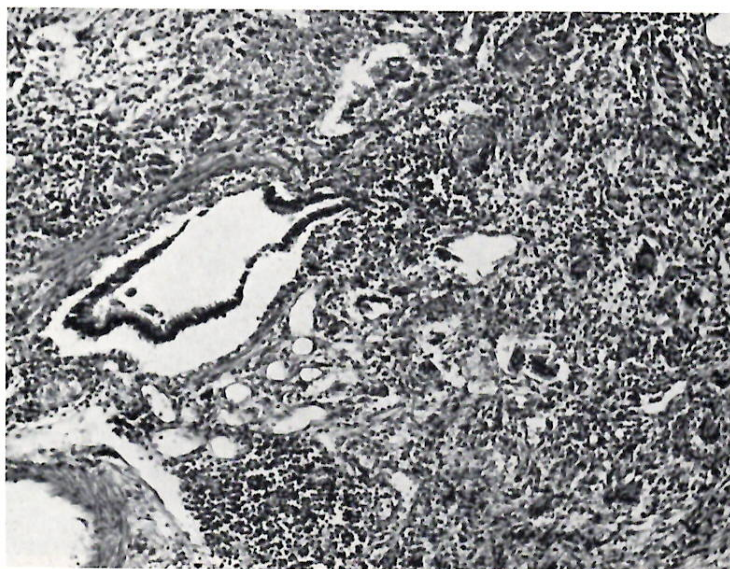


Fig. 2. Nodular proliferation of fibroblasts in the lung. Giant cells and lymphocytes are part of the cellular exudate. Magnification $\times 100$.

On physical examination, the patient was a well-developed, well-nourished 76-year-old white man with aphasia, inability to move the right arm and leg, moderate spastic weakness of the left arm and leg, and ptosis of the left eyelid. The left pupil was small but reacted to light. The right pupil was distorted and nonreactive. No bruises were present

over the head or neck. The tendon reflexes were present, but were diminished on the right. Clonus of the left ankle was elicited. No Hoffman or Babinski reflexes were present, and the patient was unaware of painful stimuli. A congenital hemangioma was seen on the right side of the face. The heart was normal to auscultation, and the lung fields were

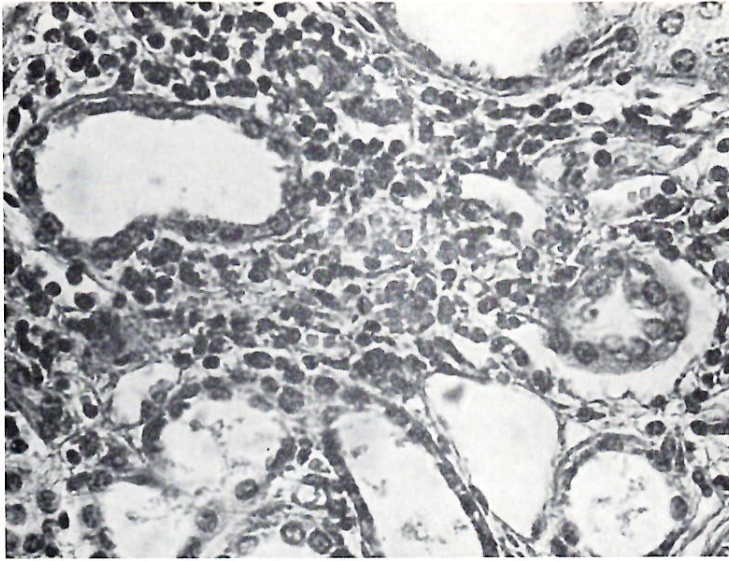


Fig. 3. Interstitial mononuclear cell infiltration between the tubules of the kidney. The exudate also consisted of a few plasma cells and eosinophils. Magnification $\times 400$.

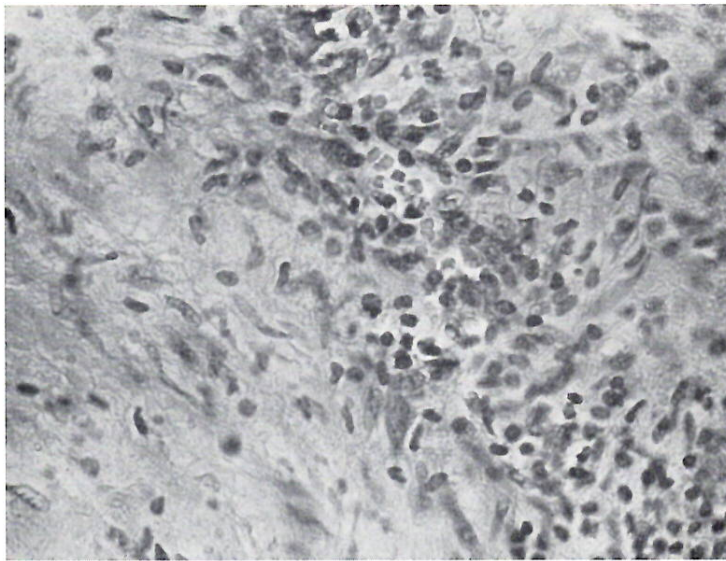


Fig. 4. Aortic valve shows fibroplasia and mononuclear cell infiltration. Magnification $\times 400$.

clear. There was some stasis dermatitis of the lower legs. The left knee was slightly swollen. The temperature was 101°F ., the pulse was 90 per minute, and the blood pressure was 140/80 mm. Hg.

Initial laboratory studies were as follows: hemoglobin 14.4 Gm.; hematocrit 41 per cent; white blood cell count 15,450 per cubic millimeter. The differential showed 83 per cent polymorphonuclear leuko-

cytes, 1 stab, 10 lymphocytes, 1 eosinophil, and 5 monocytes. Urinalysis: specific gravity 1.025; albumin 1 plus. The blood glucose was 200 mg. per cent, and the blood urea nitrogen was 89 mg. per cent. The blood serology for syphilis was negative. A portable chest x-ray film showed mild cardiac enlargement and prominence of the left ventricle. The lung fields were clear. The appearance was simi-

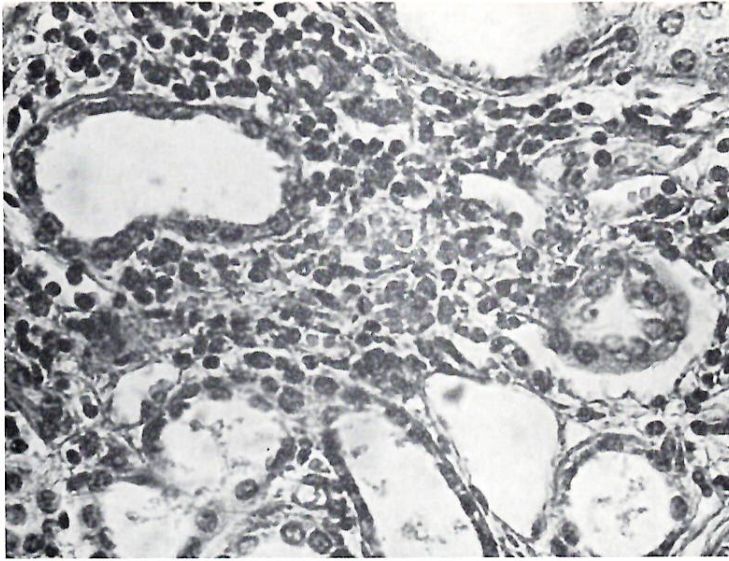


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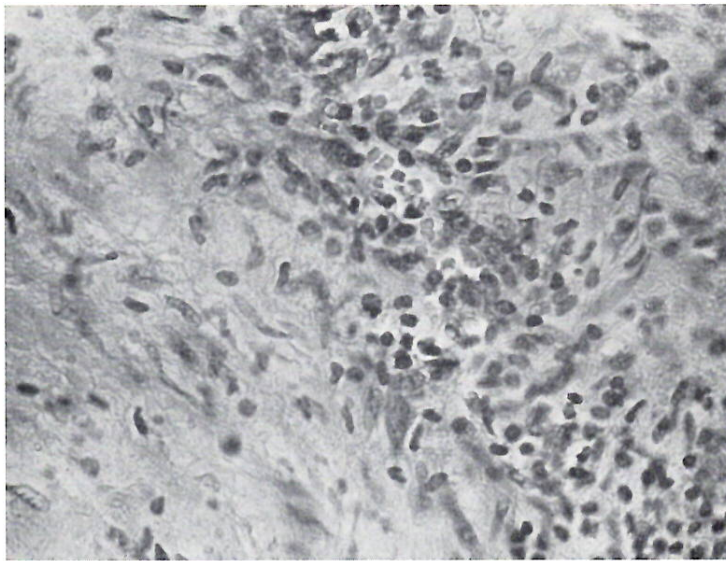


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lar to the findings on a previous chest x-ray examination performed 5 years before.

The patient was given intravenous glucose with insulin coverage, antibiotics and intramuscular Dilantin. Despite fluids and adequate renal output, the blood urea nitrogen rose rapidly to 210 mg. per cent. The temperature returned to normal on the day after admission. The pulse rate remained in the range of 80 per minute and was regular. The blood pressure varied from 140/78 to 120/70 mm. Hg throughout his stay in the hospital. The course in the hospital was one of progressive deterioration, with rapidly developing azotemia. The patient died on the seventh hospital day.

Autopsy findings. The body was that of a well-nourished and well-developed 76-year-old white man. The body length was 172 cm., and the weight was estimated to be 185 pounds. Stasis dermatitis was present in the lower extremities, particularly in the ankle region. Pressure sores and cutaneous ulcerations were seen in the dependent portions of the body.

The heart weighed 530 grams, and the left ventricular wall was 17 mm. in thickness. The myocardium was brown, with focal replacement by several pale yellowish-gray areas in the left ventricular wall. Mild fibrous thickening of the mitral and aortic leaflets was observed. Both lungs together weighed 1,120 grams, and the parenchyma was reddish-gray and of increased consistency. The parietal and visceral layers of the pleura were adherent on the right side. The spleen weighed 400 grams and had white fibrous plaques in the capsule. The liver weighed 1,500 grams. When the skull was opened, a massive subdural hematoma was found on the left side. Moderate pressure atrophy of the left cerebral hemisphere of the brain was noted.

The histopathologic study was most revealing, particularly in the material from the heart. Multiple sections from the heart showed focal replacement of muscle by granulation tissue. The granulation tissue was of the type usually seen in the protracted course of a chronic infective granuloma: fibrous tissue containing many lymphocytes, a moderate number of monocytes, plasma cells and eosinophils. The striking feature in these lesions was the presence of many multinucleated giant cells of the Langhans, myogenic, and foreign body types, in which the cytoplasm lacked asteroid, Schaumann bodies, or fungi. The inflammatory tissue was seen in the form of nodules, replacing myocardial fibers and forming an interdigital pattern with surviving heart fibers at the periphery. The epicardium was uninvolved, but subendocardial inflammatory nodules were evident. The aortic valve leaflets were slightly thickened because of fibroplasia, and infiltrations of polymorphonuclear leukocytes, lymphocytes, and plasma cells were seen in the valve substance. Giant cells were not observed in the valve. The proximal portion of the thoracic aorta contained heavy aggregations of lymphocytes and plasma cells in the adventitia.

In the lungs there were granulomatous nodules showing fibroplasia, plasma cells, and lymphocytes, in addition to young giant cells of the Langhans type. In the remainder of the parenchyma, small nodules consisting of plasma cells and lymphocytes were

observed in the alveolar walls. Acid-fast and periodic acid-Schiff stains of heart and lung tissue were negative.

The left kidney weighed 330 grams, and the right, 200 grams. The parenchyma was swollen and soft, with reduced corticomedullary demarcation. Microscopically, a heavy, diffuse, interstitial inflammatory exudate was observed, mainly in the cortex. The infiltrate consisted of lymphocytes, plasma cells, and some eosinophils; a few polymorphonuclear leukocytes were seen in some of the distal tubules.

Essential pathologic diagnoses included: old left-sided subdural hematoma, moderate pressure atrophy of the left cerebral hemisphere, chronic giant cell granulomatous nodules involving heart and lungs, moderate concentric hypertrophy of the left ventricle of the heart, chronic fibrous pleuritis on the right side, moderately advanced generalized arteriosclerosis, and acute interstitial nephritis.

Comment

Chronic giant cell granulomatous myocarditis is a rare disease and only 2 of 23 recorded cases were seen by the same investigators; the remaining 21 instances were individual case presentations. The infrequency of the lesion accounts in part for its obscure etiology and our lack of understanding of its pathogenesis. This granulomatous process must be considered to be a systemic disease since 10 of the 23 cases described involved extracardiac sites: lungs, aorta, tonsils, and Fallopian tubes.¹ It is by no means an isolated myocarditis. In our patient, the granulomatous change was seen in the lungs in addition to the heart.

This disease is seen in relatively young people; the median age of listed cases was 34 years. It has been reported in a 6-month-old baby.³ Our patient (76 years) is the oldest individual reported to have this condition; only one other case occurred beyond the fifth decade.⁴

Although our patient had the morphologic changes seen in giant cell granulomatous myocarditis, he died from unrelated disease: massive subdural hematoma, and a rapidly progressive renal insufficiency. He had no symptoms which could be related to his cardiac pathology. The lack of symptoms is not unusual, since in half of the recorded cases there was sudden death, without previous warning. It is probable that the heart muscle was involved by the granulomatous process to a lesser degree in our case than in those previously reported in the literature. If our patient

had not died from intercurrent disease, there might have been a critical progressive destruction of myocardial tissue resulting in cardiac disability. He would then have been subject to sudden death or fatal, rapidly developing congestive failure. It is also probable that the inapparent heart lesions existed for some time, since the pathologic changes were those usually associated with protracted inflammation. In the cases reviewed in the literature, the structural changes were in keeping with a chronic inflammatory disease state. Cardiac dysfunction apparently is related to the degree and location of myocardial damage, but our patient demonstrated that giant cell myocarditis may exist for some time before the terminal catastrophic illness.

No specific etiological agent has been incriminated in the pathogenesis of giant cell myocarditis. Rab and others⁵ consider the morphologic change to represent a host-tissue reaction to any one of several possible agents: *Mycobacterium tuberculosis*, leprosy, syphilis, fungi, protozoa, or helminths. To date, spirochetes, tubercle bacilli, or known fungi have not been identified in the tissues by special staining methods. We suspect that mycologic cultural studies have been inadequate, since this rare disease is usually diagnosed after microscopic study. Collyns⁶ also viewed the anatomic changes as representing a deep-seated fungus infection or a hypersensitivity state.

Our patient had a rapidly developing azotemia, which can be accounted for by the interstitial inflammatory change in the kidneys. Acute, diffuse interstitial nephritis has been regarded generally as a complication of systemic septic states of bacterial or viral origin. It has also been related to hypersensitivity or allergic reactions to sulfonamides. Lederer and Rosenblatt⁷ have described granulomatous interstitial nephritis characterized by giant cells, mononuclear cells, eosinophils, and polymorphonuclear leukocytes in the interstitial areas of the kidneys as an allergic response to sulfonamides. Although the infiltrate in the interstitium in the kidneys of our patient did not contain giant cells, there was a cellular exudate consisting of lymphocytes, plasma cells, eosinophils, and polymorphonuclear leukocytes. We ascribe

these renal changes to a possible hypersensitivity reaction, and think that this mechanism might also be responsible for the pathogenesis of the granulomatous lesions seen in the heart and lungs. This opinion would support Collyns,⁶ who suggested the possibility of a hypersensitivity reaction on the basis of observed morphologic lesions in his reported case, and Palmer and Michael,¹ who considered the same causal relationship because of the giant cell arteritis observed in the myocardium in their patient.

A clinical observation relating to a hypersensitivity etiology should be mentioned in reference to a case of granulomatous giant cell myocarditis which was reported from the Massachusetts General Hospital.⁸ It concerned a patient who had received oral penicillin therapy and developed a "serum sickness" type of reaction and an exfoliative dermatitis which suggested a hypersensitivity reaction. In the treatment of the dermatitis over a period of 5 months, the patient received steroids in dosages which were sufficient to produce a Cushinoid appearance at the time of his final illness—a rapidly developing progressive congestive heart failure with tachycardia. The necropsy showed the changes of giant cell granulomatous myocarditis with a total lack of tissue repair. Either this was not a hypersensitivity reaction with respect to the pathogenesis of the myocarditis, or the steroids were incapable of reversing the process. However, from a therapeutic viewpoint, if this entity is suspected, it seems to be rational that treatment should include the use of large dosages of steroids. This seems to be especially true because of the catastrophic course of the disease.

Summary

A 76-year-old man who was known to be an epileptic died from a massive subdural hematoma and a rapidly progressive renal insufficiency. Incidental findings at necropsy were the histopathologic changes of giant cell granulomatous myocarditis and granulomatous nodules in the lungs. The patient had never had symptoms relating to his underlying cardiac pathology. It is postulated that the degree of myocardial involvement was not extensive enough to

interfere with cardiac function, and an intercurrent fatal episode precluded the usual progression of this disease. Chronic giant cell granulomatous myocarditis is part of a systemic disease of unknown etiology. However, the renal lesions of acute interstitial nephritis seen in our patient lend support for a hypersensitivity mechanism. We think that this is the oldest patient to be reported on, and the only one in whom the cardiac pathology was not the cause of death.

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