Idiopathic giant cell myocarditis—a distinctive clinico-pathological entity

M. J. Davies, Ariela Pomerance, and R. D. Teare

From the Departments of Pathology and Forensic Medicine, St. George's Hospital, and Department of Pathology, Northwick Park Hospital

Eleven cases of idiopathic giant cell myocarditis are described. The pathological features are unmistakable with serpiginous areas of myocardial necrosis, at the margins of which giant cells can be seen on histological examination. The aetiology of the condition remains obscure but associated pathology suggests that altered immunity may be a factor. The rapid clinical course is, however, highly suggestive of an infective cause though none has been found.

This paper draws attention to a fatal form of acute myocarditis characterized by serpiginous areas of myocardial necrosis as seen at necropsy and giant cell formation observed histologically. The giant cells are derived from viable muscle fibres at the periphery of the areas of necrosis and the histological picture is distinct from the giant cell granulomas of sarcoidosis or rheumatic fever. The best name for this entity seems to be idiopathic giant cell myocarditis.

Subjects and methods

A review of hearts collected by, or submitted to, us over the past 9 years showed 11 cases of idiopathic giant myocarditis. Clinical details are given in the Table. Fresh cardiac tissue was available for virological studies in 7 and ultrastructural study in 3 cases. Serum obtained at necropsy was screened for toxoplasma antibodies in 7 patients but was not suitable for detection of autoantibodies to muscle or thyroid.

In attempting virus isolation, ground-up fresh myocardium was used in conjunction with primary cell lines of human embryonic kidney and rhesus monkey kidney. Toxoplasma titres were estimated by the toxoplasma dye test (Sabin and Feldman, 1948). Material for electron microscopy was fixed in gluteraldehyde with post-fixation in osmium tetroxide by entirely conventional technique (Sabatini, Bensch, and Barnett, 1963). Sections cut on a Reichert OMU2 ultramicrotome were stained in uranyl acetate in 50 per cent alcohol for 20 minutes followed by lead citrate solution and examined in a Zeiss electron microscope (EM 9S).

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Results

All cases showed serpiginous areas of necrosis in the myocardium allowing an easy naked eye diagnosis at necropsy (Fig. 1). Both ventricles were equally affected. In 3 cases atrial muscle was heavily involved, the remaining hearts showing only microscopical atrial lesions. Where the clinical course exceeded a few days, left ventricular dilatation and mural thrombus formation were seen. No pericarditis or endocarditis was noted.

Histological examination confirmed the presence of areas of muscle necrosis with giant cells at the margins. Sections taken in a plane longitudinal to muscle fibres (Fig. 2) show these giant cells to be contiguous with adjacent muscle cells and probably to be derived from them. Ultrastructural studies of 3 cases, greatly marred by post-mortem artefact, showed the giant cells to contain myofibrils.

Within the areas of necrosis a florid histiocytic and eosinophilic cell infiltrate was consistently seen, the adjacent myocardium being without abnormality. Routine necropsies on these patients revealed a wealth of additional systemic disease including two thymic tumours. One was anaplastic, possibly an alveolar rhabdomyosarcoma, the other a spindle cell thymoma. One patient had systemic sarcoidosis with pulmonary, nodal, splenic, and liver granulomata. Two had a severe degree of thyroiditis of the Hashimoto type; in one of these thyrotoxicosis had been present some years previously. No patients had received drug therapy within 6 months of death other than thyroxin in the 2 cases of thyroid

TABLE Clinical and pathological data

Case No.	Sex	Age (yr)	Presentation	Electrocardiogram	Associated pathology
1	F	47	10 days dyspnoea	Left-bundle-branch block; atrial fibrillation	Thyroiditis
2	M	49	Sudden death watching TV	—	Sarcoid liver, spleen, lung
3	F	31	Dyspnoea, mass on chest x-ray; 3-wk course	—	Thymic tumour (sarcoma)
4	M	29	'Flu' for few days; sudden death while running	—	*
5	F	24	6 days of dyspnoea/chest pain	Left bundle-branch block, bizarre QRS, ventricular ectopics	*
6	M	54	Sudden death	—	*
7	M	19	7 days of dyspnoea	Supraventricular tachycardia, bizarre QRS	*
8	F	19	Sudden death	—	*
9	F	36	10 days of dyspnoea	Ventricular left bundle-branch tachycardia, atrial fibrillation	*
10	F	54	6 days, chest pain/dyspnoea	Wide QRS, complete heart block	Thyroiditis
11	F	72	Sudden death	—	Spindle cell thymoma

* No abnormality found outside heart in routine necropsy.

disease. No viruses were isolated in tissue culture nor were any particles resembling virus bodies seen by electron microscopy. The toxoplasma titre did not exceed 1/64 in any case.

Discussion

The disease in our series predominantly affected young to middle-aged adults (Table) in agreement with other published reports (Parrish, 1965; Dilling, 1956); an isolated case is recorded in infancy (Goldberg, 1955). The clinical course is rapid with sudden onset. The longest survival in our series was 10 days. The case recorded by Parrish (1965) was symptomatic for one month. Sudden death is common, with this feature as the presenting symptom in 5 of our cases. Patients admitted to hospital are found to have fever with electrocardiographic evidence of widespread acute myocardial damage and irritability. When estimated, the serum enzymes are raised (Parrish, 1965) though we do not have data on our own cases. There is little clinical difference between this form of myocarditis

FIG. 1 Serpiginous areas of necrosis visible to the naked eye in the myocardium of the left ventricle at the base of the anterolateral papillary muscle. A central dark component of necrotic muscle is surrounded by lighter enclosing zones of inflammatory cells.

FIG. 2 Histological section (Haematoxylin and eosin, $\times 120$), showing infiltration of the myocardium with inflammatory cells. An elongated giant cell (arrows) contains many vesicular nuclei characteristic of a myogenic origin.

and non-specific acute myocarditis thought to be of viral origin, except for an unusually rapid course. Whitehead (1965) in a necropsy study of 18 cases of fatal acute myocarditis found 3 which belonged to the idiopathic giant cell type.

The distinctive and interesting feature of this form of myocarditis is the formation of giant cells from myocardial muscle cells. The reaction is reminiscent of skeletal muscle regeneration following injury. The histological picture is quite distinct from the follicular granulomata of sarcoid (Fleming, 1973), or the interstitial granulomata of rheumatic fever and its variants (Husband and Lannigan, 1965; Gillie and Fox, 1968), or the vascular lesion of Wegener's granulomatosis in the myocardium (Walton, 1958; McCrae and Childers, 1964). The name of Fielder (Magalini, 1971) has been associated with a progressive fatal myocarditis but his description was essentially clinical and, while it is likely that some of his cases were of the idiopathic giant cell type, the eponym is best avoided.

It must be admitted that the aetiology of this condition remains totally obscure. The sudden onset, fever, and inflammatory response could suggest viral or other infection but we, like others, have failed to isolate or obtain serological evidence of any organism. The significance of this negative finding however is dubious with postmortem material. Initiation of giant cell formation in cells affected by virus is well recognized in other tissue.

An association with thymomas usually of the spindle cell type is well recognized (Funkhouser, 1961; Langston, Wagman, and Dickenman, 1959; McCrea and Jagoe, 1963). The sarcoma seen arising from the thymus in Case 3 may represent a histogenesis from the striated muscle found in the infant thymus and to our knowledge an association of this tumour with giant cell myocarditis is not recorded. An association of idiopathic giant cell myocarditis with disseminated lupus erythematosus is recorded (Funkhouser, 1961) and with thyrotoxicosis (Hudson, 1970).

Sarcoidosis affecting the myocardium usually retains its easily recognized follicular granulomata. The occurrence of idiopathic giant cell myocarditis in patients with systemic sarcoidosis (Dilling, 1956) is recorded and has been seen once in our series.

It is tempting to suggest that the common factor present in the diverse conditions associated with idiopathic giant cell myocarditis is altered or depressed immunity allowing myocardial infection by viruses or other agents. Failure to demonstrate an infective cause at necropsy cannot be regarded as excluding this possibility. It is unlikely that an autoimmune response against cardiac muscle could be initiated with such rapidity as the clinical course suggests. The finding of striated muscle in the normal human infant thymus (Henry, 1968), however, has led to speculation that an autoimmune process against cardiac and skeletal muscle could occur in thymic disease (Burke, Medline, and Katz, 1969). While an association with thymic neoplasms is recorded it is rare. In 101 thymomas submitted to the thymoma panel in London only one (Case 11) had a giant cell myocarditis (N. F. C. Gowing, 1974, personal communication), and with the profound clinical effect produced by this form of myocarditis the association is not likely to have escaped notice.

The present study is incomplete in many aspects, being essentially a study of forensic necropsy material from scattered centres. With clinical awareness of the condition, determined efforts to prove or disprove a viral aetiology and estimation of a wide range of autoantibodies are required.

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- Requests for reprints to Dr. M. J. Davies, Department of Histopathology, St. George's Hospital Medical School, Blackshaw Road, London SW17 0QT.