Acute idiopathic interstitial myocarditis: case report with special reference to morphological characteristics of giant cells

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SUMMARY Necropsy findings of an acute fatal case of idiopathic interstitial myocarditis were reported. The patient was a 33 year old housewife who had acute cardiac failure on the sixteenth day after the onset of the disease. Necropsy showed important pathological changes confined to the heart. Both ventricles were affected by confluent granulomas with an ill defined patchy appearance. Histologically these lesions consisted of round cells, histiocytes, eosinophils and myogenic giant cells. The findings were compatible with those of interstitial myocarditis associated with a proliferation of giant cells. Both atriums were also affected to a minor extent, detectable only by histological examination. Electron microscopy and cytochemistry showed that most giant cells noted in the lesion showed myofibrils and primary lysosomes in the cytoplasm. Giant cells were positive for myoglobin.

Though the macrophage origin of the giant cell in this disorder has been emphasised in a recent report, these cytological results suggest that giant cells observed in the cardiac granulomatous lesions of this case were mainly myogenic in origin.

Various infectious disorders are known to induce granulomatous lesions in the myocardium, which are associated with the appearance of giant cells.^{1,2} These disorders are not necessarily fatal, and some cases can be cured. An acute idiopathic form of interstitial myocarditis, a rare primary disorder of the heart, is often fatal and is accompanied by extensive degeneration and necrosis of the myocardium and a granuloma like lesion consisting of round cell infiltration, histiocytosis, and eosinophilia. A proliferation of giant cells of both histiocytic and myogenic type, with a certain variation in number according to the case, is also often noted in this disorder.^{1,2} The important change is confined to the heart and has been named as either isolated or idiopathic interstitial myocarditis. Because of the unique morphology of its myocardial granulomatous lesion, the disorder is commonly referred to as giant cell myocarditis. About 40 cases of an acute idiopathic form of giant cell myocarditis have been reported worldwide.^{3,4}

Careful review of these reported cases showed that nearly half were probably cardiac sarcoidosis.⁵ Characteristic giant cells observed in acute idiopathic interstitial myocarditis may originate from degenerating myocardial cells and myocardial interstitial histiocytes,¹ their origin, however, is still somewhat controversial. Filamentous materials resembling degenerated myofibrils detectable ultrastructurally in these cells⁶ were interpreted either as degenerating myofibrils of the myocardial cell⁷ or phagocytised myofibrils of macrophages.⁸⁻¹⁰ Histochemically, the lysosomal activity of these giant cells did not help to distinguish their origin.¹⁰ A recent immunohistochemical study showed the presence of anti-macrophage and anti-Leu 3a (anti-T cell) antigens in giant cells and suggested that they originated from macrophages.¹⁰

This paper adds a further case to the reported cases of acute idiopathic interstitial myocarditis and presents evidence for the myogenic origin of giant cells, particularly on the basis of their ultrastructural and immunohistological characteristics.

Case report

CLINICAL HISTORY

A 33 year old Japanese housewife had been healthy and had no history of allergic reaction to commonly prescribed drugs. She had no history of recent travel abroad. Her husband and two children were all healthy. In September 1984 she felt discomfort in the epigastric region after breakfast. On a visit to a neighbouring hospital, cardiomegaly and arrhythmia were pointed out. She then developed syncope for five minutes when she went upstairs at home. She was immediately taken to a local hospital. Electrocardiography showed an increase in S-T segment in II, III, aVf and V1-2, premature atrial contraction, and premature ventricular contraction and sinus tachycardia (120/minute). Digitalis and lidocaine were ineffective. She was transferred to Oume Municipal General Hospital. On admission, her physical condition was as follows: body temperature 36.7°C; cardiac rate 96/minute; respiratory rate 14/minute; blood pressure 90/70 mm Hg. Congestion of both lungs and enlarged cardiothoracic ratio (67%) were found on chest radiography. Central venous pressure was slightly raised (17 cm water). An electron cardiogram

showed first degree A-V block (PQ interval 0.26 seconds), disturbance of intraventricular conduction (QRS 0.09 seconds), and low voltage. Changes in serum enzyme activities were unimportant: creatine phosphokinase 107 IU/l (normal range = 24-170), glutamic-oxaloacetic transaminase 28 IU/l (normal range: 0-40), glutamic pyruvic transaminase 16 IU/l (normal range: 0-35), except for slightly raised lactate dehydrogenase activities (751 Wroblewski units, normal range: 100-450). Data on peripheral blood showed (red blood cells 481×10^4 , white cells 7600, haemoglobin concentration 11.2 g/dl, haematocrit 33.5%, platelets 16.1×10^4) and serum (rheumatic factor test negative, *Treponema pallidum* haemagglutination test negative, C-reactive protein 1+) showed no clinically important changes. Tests for tuberculin and Kveim reactions and estimations of antibody titres for viruses were not performed. Primary myocardial disease was suspected clinically, and the patient was conservatively treated by furosemide (80 mg/day) and dopamine (4-5 μ g/kg/minute). Right pneumothorax occurred and a continuous drainage was carried out. The pneumothorax improved four days later. Ventricular tachycardia (150/minute) then appeared and bradycardia followed (40/minute). Her

Fig1 Cross section of ventricles. Note slight to moderate dilatation of bilateral ventricles with diffuse thinning of myocardium. No focal necrosis is observed.

Fig2 Low power view of part of left ventricle showing diffusely distributed patchy granulomas (*). Changes are important at external myocardial layer adjacent to epicardial fatty tissue. Endocardial side is at the bottom. (Azan stain.) $\times 8$.

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blood pressure became unmeasurable. A transient pacemaker was inserted but she died on September 21, 1984, 16 days after the onset of the disease.

Pathology

Necropsy was carried out two and a half hours after death. Notable pathological changes were confined to the heart. No clinically important changes were observed in other viscera.

The heart weighed 320 g. There was a small amount of pericardial effusion (60 ml) without apparent signs of pericarditis. Both ventricles were moderately dilated. The volume of the cardiac chambers was measured by a clay moulding method, and the data obtained were as follows: left ventricle 57.8 ml; right ventricle 72.9 ml; left atrium 28.1 ml; right atrium 49.7 ml. The wall thickness of the heart was at the low limit of the normal range: left ventricle 8.0 mm; right ventricle 2.0–2.5 mm. The circumference of the valvula annuli was within the normal range. No abnormality was found in any cardiac valve. Both coronary arteries showed minimal sclerosis. A bean sized fresh thrombus was attached to the endocardium of the left ventricular apex. On the cut surface, patchy lesions of

up to a rice grain size, which were vaguely bordered and appeared greyish-white in colour, were spread diffusely and occupied about one third to a half of bilateral ventricle volumes (figs 1 and 2). Overall, neither scars nor necrotic foci were detectable in the myocardium.

Histologically patchy lesions were noted throughout the myocardium and consisted of granulomas of various sizes spread extensively through both ventricles (figs 2–4), the left atrium slightly, and the right atrium only at the appendage. The disease in both ventricles manifested itself more noticeably in the myocardium of the epicardial side; the epicardial fat tissue was only partially affected (fig 2). Papillary muscles of both ventricles were affected. No granulomatous lesions were noted in the chorda tendinae and cardiac valves. Major cellular elements found in the granulomatous lesions were small to medium sized lymphocytes and histiocytes (figs 3 and 4). A moderate number of eosinophils and plasma cells were also noted, but almost no neutrophils. Multinucleated giant cells of 25–90 × 10–20 µm in size, having up to 20 nuclei were found throughout the granulomatous foci, particularly at the periphery where a close contact to undamaged myocardial cells was speculated. In

Fig 3 General view of granulomatous changes observed adjacent to degenerating myocardial cells (right upper corner). Details of cellular reaction in marked area of this picture are shown in fig 4. (Haematoxylin and eosin.) × 155.

Fig 4 Granulomatous changes consisted of round cells, fibroblasts, and giant cells (arrow). Giant cells are commonly seen at parallel to degenerating myocardial cells (*). (Haematoxylin and eosin.) × 185.

granulomatous foci atrophy, swelling, and degeneration of muscle fibres were common (figs 3 and 4). Proliferation of fibroblasts and capillaries and new deposition of collagen were evident. Neither vasculitis nor neuritis was noted.

Neither granulomatous lesions nor angitis were found in other organs. A 2 × 1 cm sized scar was found in the right apex of the lung (230:310 g) (weight of left lung 230 g, right lung 310 g); focal lymphocytosis was also noted. Organising pneumonia of right

Figs 5–7 Three types of multinuclear giant cells distinguished by nuclear position. Figs 5 and 6 were taken from haematoxylin and eosin stained sections, and fig 7 was taken from immunohistochemically stained section (PAP method, myoglobin.) × 820.

- Fig 5 Elongated type which often communicates with degenerating muscle cells.
- Fig 6 Giant cell with centrally located multiple nuclei.
- Fig 7 Giant cell with circularly arranged multiple nuclei. Myoglobin is weakly positive in upper part of the cytoplasm of giant cell.

Table 1 Immunohistochemical differences of giant cells shown by PAP method

	Types of giant cells (incidence in %)				Sarcoidosis	Langhans' type	Foreign body type	Touton type
	I	II	III					
Myoglobin*	(A) 52 (B) 32 (C) 16	24 8 0	22 14 10	6 10 6	(-)	(-)	(-)	(-)
Lysozyme*	(A) 8 (B) 42 (C) 50	0 6 20	4 26 18	4 10 12	(++)	(+++)	(+)(-)	(++)(+)
IgG**	(+)(+)(+)				(+)	(+)	(++)(-)	(+)(-)
IgA**	(+)(+)(-)				(+)	(-)	(++)(-)	(+)(-)
IgM**	(+)(-)(-)				(+)	(-)	(++)(-)	(+)(-)

Sources of reagents: *DakoPatts Inc. **Boehringerwerke. A, B, and C (A = definitely positive, B = faintly positive, C = negative), staining intensity = (-) negative, (+) weakly positive, (++) moderately positive, (+++) strongly positive.

Fig 8 Low power view of multinucleated giant cell of elongated type. Cell was preserved poorly due to cadaverous change. Parts of cytoplasm, (square) and (arrow) were further enlarged and are shown in figs 9 and 10, respectively. (Lead citrate and uranyl acetate.) $\times 1960$.

Fig 9 Higher magnification of cytoplasmic portion of giant cell shown in fig 8. Myofibrils (Mf) in cytoplasm are shown. Mb: cell membrane. $\times 8480$.

Fig 10 Dense structure of cytoplasm consisting of condensed (degenerating) myofibrils (Mf). M = mitochondria. $\times 17000$.

Discussion

Acute idiopathic interstitial myocarditis, a diffuse type of Fiedler's myocarditis,^{11 12} has been distinguished from other forms of myocarditis observed in systemic disorders, including sarcoidosis, infectious, toxic, and allergic diseases. Because of the presence of occasional multinucleated giant cells in the myocardial lesions of this disease,¹³ the term isolated giant cell myocarditis is often applied, particularly in western reports. As the appearance of giant cells is related to non-specific myocardial lesions and is less common in acute idiopathic interstitial myocarditis the term giant cell myocarditis has not been used in this report.

The pathogenesis of this disease is unknown,¹⁴ but viral infections have been speculated.¹⁵ The acute fatal course of a case of an isolated cardiac lesion, compatible histologically with interstitial myocarditis, led to the final diagnosis. No granulomatous foci, which would suggest sarcoidosis, were detected in systemic organs examined both grossly and histologically. Looking at the available pathological anatomical data, our case resembles Friedler's myocarditis reported by Parrish¹⁶ and giant cell myocarditis reported by Suganuma *et al*¹⁷; more extensive myocardial disease was reported in the former case.

In general, the term "giant cell myocarditis" is loosely applied to granulomatous myocardial lesions associated with the appearance of giant cells: any granulomatous lesion that affects the myocardium can expect to form giant cells.^{14 18} The appearance of giant cells in myocardial granulomatous lesions is possibly related to a reparatory process of damaged myocardial cells. Intervention of macrophages of both local (histiocytes) and blood (monocytes) origin, with certain variations in numbers, reflecting the stage of the disease, may occur.

In an earlier stage giant cells originating from degenerated or regenerating myocardial cells, or both, may predominate, in contrast to specimens of a later stage, in which macrophages may be observed more commonly following an advanced reparative process. It is likely that the controversial problem of the origin of giant cells in interstitial myocarditis is related, at least in a part, to morphological differences between granulomatous lesions, relating to the repair stage of the disease. The presence of giant cells in granulomatous lesions of the myocardium thus does not suggest any definitive pathogenesis. Rather, the topography of the granuloma, which is confined to the heart, may be more reliable and specific to define the disorder.

The origin of giant cells is one of the most popular topics concerning interstitial myocarditis. Both myogenic and macrophage origins for giant cells have

already been considered.^{1 2 14} Although a myogenic origin for giant cells is favoured, both foreign body and Langhans' type giant cells have also been suggested.^{14 19} The morphological grounds for the myogenic origin of giant cells are as follows: (i) parallel position of giant cells and muscle fibres; (ii) a direct contact between giant cells and muscle cells^{17 18 20 21}; (iii) the presence of a smooth transition from a giant cell to a muscle cell; (iv) myofibrils in the cytoplasm of giant cells^{6 22 23 24}; (v) lipofuscin granules in the cytoplasm of giant cells.¹³ These criteria have been drawn from data obtained during regeneration of the skeletal muscle after injury.^{4 23} Some argue that the latter three criteria are related to phagocytosis.^{10 18}

We morphologically classified the giant cell of this case into three types. The type I giant cell satisfies all morphological criteria stated above and thus can be regarded as a myogenic type. Though giant cells of the two other types also satisfy the criteria for the myogenic origin, the type II giant cells resemble foreign body giant cells. Morphological differences were seen between the type III giant cell and giant cells observed in tuberculosis and sarcoidosis. The myogenic origin of most giant cells observed in our case was further confirmed ultrastructurally and immunohistochemically. An electron microscopical examination showed a close association between degenerated muscle fibres and the cytoplasm of the giant cell, confirming earlier an observation made by Pyun *et al*.⁶ The presence of myoglobin was shown immunohistochemically in over 50% of giant cells in our case, suggesting that most of the giant cells were of myogenic origin.

Recently immunocytochemical methods have been applied to define the macrophage nature of giant cells observed in interstitial myocarditis.¹⁰ Although not tested in this study, Theaker *et al*¹⁰ showed two different antimacrophage antibodies (EMB 11 and KB 90) in giant cells using a monoclonal antibody method. They reported that both desmin and Ki 67 were negative in giant cells, except for a positive Ki 67 reaction in the nuclei of lymphocytes and mononuclear phagocytes. Lysozyme activity was nearly absent in our case, which agrees with the findings of most other cases reported,^{7 8 10} except that a positive reaction was noted in one case.⁹ This case may be regarded as specific, as the giant cells of this case showed no elongated forms (type I of our case), no transitional forms to muscle cells, and a negative cytochemical reaction to myosin and creatine phosphokinase. Negative lysozyme activity, however, does not completely exclude a histiocytic origin for giant cells, because some macrophages are known to appear negatively.²⁵ Cellular immunity is required to induce the lysozyme activity.⁸ Perhaps the positive lysozymal activity noted in that case⁹ was related to underlying

immunological abnormality caused by chronic active hepatitis with positive antinuclear antibody.

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