Virchows Arch [Pathol Anat] (1985) 408:307–312

*Virchows Archiv A*


# Familial congestive cardiomyopathy with nemaline rods in heart and skeletal muscle

**Joan G. Jones and Stephen M. Factor**

Department of Pathology, Bronx Municipal Hospital Center
Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461, USA

**Summary.** Primary familial cardiomyopathy, once exclusively associated with hypertrophic disorders, is now recognized to occur in a dilated or congestive form. In some instances, characteristic myocellular inclusions of varying morphologies have been identified. Nemaline rods are inclusions which typically have been linked with a rather benign and nonprogressive congenital myopathy. We report finding myocellular inclusions consistent with nemaline rods in two brother who died with congestive cardiomyopathy. Although there was no history or clinical evidence of a myopathy, characteristic nemaline rod inclusions were also identified in the skeletal muscle of one sibling.

**Key words:** Familial cardiomyopathy – Nemaline rods – Myopathy

Most commonly, the term familial or genetic cardiomyopathy has been associated with a hypertrophic disorder. With the exception of cardiac involvement in some forms of inherited muscular dystrophy and storage disease, primary dilated or congestive cardiomyopathy is rarely familial. Recently, however, familial clusterings of congestive cardiomyopathy have been reported; in some, myocellular inclusions have been identified as Lafora-like bodies or desmin-type intermediate filaments (Rosai and Lascano 1970; Porte et al. 1980).

Nemaline myopathy, which is characterized by electron-dense inclusions of Z-band material, was originally described as a congenital myopathy with a rather benign and nonprogressive course (Shy et al. 1963; Conen et al. 1963). Subsequently, fatalities in children, as well as sporadic adult onset cases have been reported (Shafiq et al. 1967; Matsuo et al. 1982; Engel 1966; Brownell et al. 1978). Cardiac involvement, however, has only been observed once (Meier et al. 1984).

This current presentation was prompted by autopsy findings in two brothers who died from congestive cardiomyopathy. The finding of inclusions consistent with nemaline rods in the skeletal and cardiac muscle

*Offprint requests to:* S. M. Factor at the above address

of one brother led to a review of autopsy data on the younger sibling who died four years before. Identical myocardial inclusions were found in this case, supporting the diagnosis of familial nemaline rod cardiomyopathy.

## Case report

D.R. was a 69 year old male of Italian descent with multiple admissions for increasing heart failure. The patient had a 15 year history of progressive shortness of breath and dyspnea on exertion with documented cardiomegaly by chest X-ray, left atrial and left ventricular enlargement by echocardiogram, and left ventricular hypertrophy on electrocardiogram from the time of initial evaluation. Symptoms progressed despite treatment with digitalis and diuretics. When atrial fibrillation developed, a repeat echocardiogram was performed which showed additional right ventricular enlargement and midsystolic closure of the aortic valve, suggestive of mitral regurgitation. Five months prior to the current admission, the patient was enrolled in an experimental cardiac drug study in an attempt to control his symptoms. Clinical response, however, was transient, and the patient was admitted again for increasing shortness of breath and exertional fatigue.

Examination revealed an afebrile normotensive male in atrial fibrillation. Cardiac examination was notable for a laterally displaced apical impulse with left parasternal heave, an audible S3 and accentuated P2, and a II/VI systolic murmur radiating from the apex to the axilla. Jugular venous distention, hepatomegaly, peripheral edema, and bibasilar rales were present. Although the patient initially showed clinical improvement with aggressive medical management, on day 4 he developed pneumonia. Antibiotic therapy was initiated but without adequate response. The patient's cardiac status deteriorated, and despite treatment with vasopressors and unloading agents, the patient died several days after admission.

*Autopsy findings.* Autopsy revealed a 900 gm heart with four chamber hypertrophy and dilatation. There was only minimal evidence of coronary artery disease. Multiple sections of myocardium from both atria and ventricles showed generalized myocellular hypertrophy and vacuolar degeneration, focal replacement fibrosis, and diffuse interstitial scarring. In the central portion of some vacuolated cells, deeply eosinophilic, hyaline, rounded inclusions were detected (Fig. 1 A, B). The inclusions stained positively with trichrome, PTAH, elastica, and reticulin; PAS gave a weakly positive response which was diastase resistant. Although electron microscopy revealed nonspecific features consistent with cardiomyopathy – myocellular hypertrophy, increased numbers of mitochondria, and focal aggregations of actin-like filaments – attempts to localize the inclusions seen on light microscopy were unsuccessful.

Multiple sections of skeletal muscle, including psoas and diaphragm, also demonstrated many similar amorphous, intensely eosinophilic inclusions (Fig. 1 C, D). These inclusions were only rarely seen in degenerating or atrophic fibers, and the surrounding vacuolization noted in myocells was not present. The staining characteristics of the inclusions were identical to those found in the myocardium; they also stained strongly with toluidine blue in one micron Epon-embedded sections (Fig. 1 E). On electron microscopy the inclusions appeared as electron-dense filaments aggregated in a Z-band location, aligned parallel to the myofibrils where they exhibited a longitudinal periodicity of 90–100 Å (Fig. 1 F).

*Case report.* J.R., a 53 year old white male, was admitted in 1976 for syncope. The patient gave a history of rheumatic fever at the age of 8 and reported taking digitalis for 25 years. Periodically there had been admissions for cardioversion of atrial fibrillation. Symptoms of congestive heart failure were present but not prominent in the patient's clinical course. There was no history of formal cardiac status evaluation.

On admission the patient was afebrile, normotensive, with an irregular pulse rate of 180. Cardiac examination revealed cardiomegaly, an S3 gallop, a III/VI systolic murmur radiating from the apex to the axilla, and a II/VI ejection murmur at the left sternal border. The lungs were clear, but the extremities showed massive edema. Chest X-ray revealed cardiomegaly without pulmonary vascular congestion, and electrocardiogram showed atrial fibrillation, left bundle branch block, and left ventricular hypertrophy.

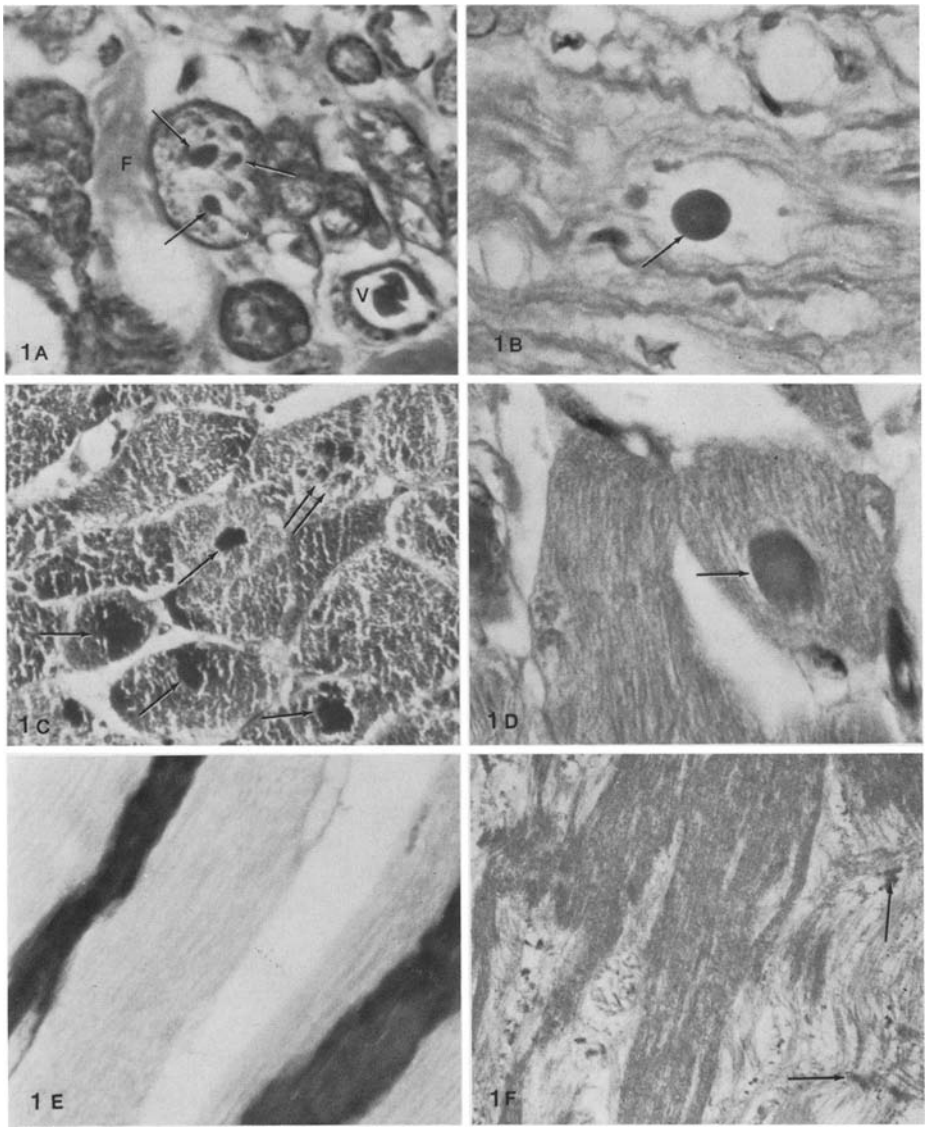


**Fig. 1 A** An area of left ventricular myocardium in which the myocytes are sectioned transversely, reveal focal vacuolization (*V*), and are surrounded by interstitial fibrosis (*F*). The central cell has multiple small trichrome-positive sarcoplasmic inclusions (arrows). Masson's trichrome, ×400. **B** This section of atrium reveals diffuse myocyte vacuolization and interstitial fibrosis. There is a single, densely eosinophilic, hyaline inclusion (*arrow*) in the central vacuolated cell. Hematoxylin-eosin, ×400. **C** A section of psoas muscle with numerous central or peripheral trichrome positive inclusions (*arrows*). One cell (*double arrows*) has multiple sarcoplasmic inclusions similar to those seen in **A**. Masson's trichrome, ×150. **D** A section of diaphragm reveals a PAS positive, diastase resistant inclusion (*arrows*) in one myocyte, ×400. **E** A toluidine blue stained, Epon-embedded section of longitudinally oriented diaphragmatic muscle. Two adjacent cells have deeply staining central inclusions running parallel to the myofilaments, ×1000. **F** This electron micrograph of a diaphragmatic myocyte reveals streaming electron-dense filaments, which corresponds to the inclusion seen by light microscopy. The material appears to be focally associated with several irregular Z-discs seen in portions of 2 sarcomeres (*arrows*). The apparent distortion is probably secondary to autolysis, ×*15,000*

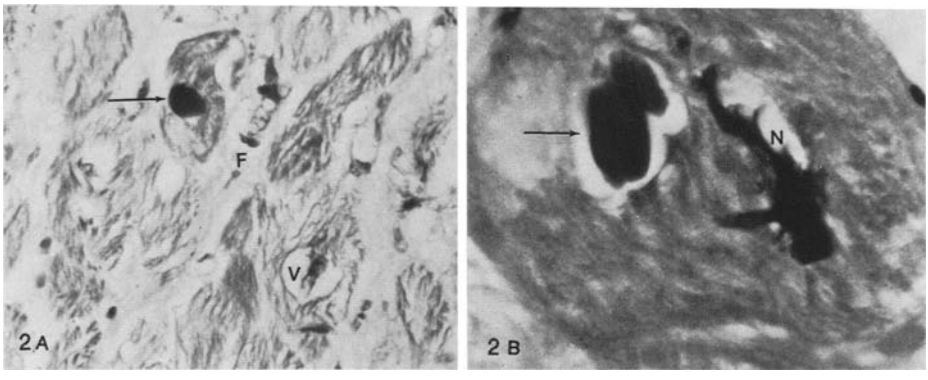


**Fig. 2A** A section of left ventricular myocardium reveals vacuolated *(V)* and degenerated myocytes, and interstitial fibrosis. A dense trichrome positive inclusion is seen in one cell (*arrow*). Masson's trichrome, *× 150*. **B** An atrial myocyte seen at high magnification. The cell is hypertrophied and it has an irregular, distorted nucleus (*N*). Within a vacuole peripheral to the nucleus, there is a lobulated, deeply eosinophilic inclusion (*arrow*), which corresponds closely to that seen in the atrial cell from case 1. Hematoxylin-eosin, *× 1,000*

The patient's hospital course was inexorably downhill. On day 2, he became febrile, developed gastrointestinal hemorrhage, and was noted to have liver function tests consistent with acute congestive hepatic necrosis. Antibiotic treatment for a gram negative urinary tract infection was instituted, and the patient was successfully cardioverted. Despite these measures, hemodynamic compromise, including episodic hypotension and decreased urinary output, persisted, and on day 4 the patient died.

*Autopsy findings.* Autopsy revealed a 700 gm heart with four chamber enlargement. The mitral annulus was dilated secondary to the marked left atrial and left ventricular changes. Although the mitral valve showed nonspecific thickening of the anterior leaflet with focal scarring and fusion of several chordae, its appearance was not consistent with chronic rheumatic heart disease. Review of myocardial sections revealed myocellular hypertrophy, interstitial fibrosis, and extensive vacuolar degeneration. More notable, however, were intracellular inclusions similar in appearance to those found in the patient's brother (Fig. 2A, B). Special stains of the inclusions produced an identical reaction pattern to that seen in the first case. Unfortunately, electron microscopy of formalin fixed tissue did not reveal inclusions, and no skeletal muscle was available for examination.

## Comments

In neither of these cases was there evidence of a viral myocarditis. There was no history of alcohol abuse or common environmental or occupational exposure. Neither patient had a history of neuromuscular complaints, and no formal testing in this regard was ever performed. Although each of these patients had a family of his own, the progeny have been lost to follow-up. The patient's mother died from undiagnosed cardiac disease.

## Discussion

The autopsy data suggest that these brothers suffered from an unusual inclusion body congestive cardiomyopathy, with skeletal muscle involvement

documented in one. There are several possible mechanisms to be considered as the cause of cardiomyopathy in two siblings. In terms of congenital myopathies associated with myocardial degeneration, there is no clinical or pathological evidence to support the diagnosis of typical muscular dystrophy or storage disease. Neither is there any indication of a commonly shared environmental insult. With regard to types of inclusion body disease, the deeply eosinophilic inclusions and their ultrastructural appearance are not consistent with entities such as mitochondrial myopathy (Hubner and Grantzon 1983), basophilic degeneration (Rosai and Lascano 1970), or the intermediate filament accumulations observed by Porte et al. (1980). The staining characteristics and Z-band localization of the electron dense inclusions seen in our patients are most consistent with what have been described as nemaline rods (Shy et al. 1963; Conen et al. 1963; Shaftiq et al. 1967; Matsuo et al. 1982; Engel 1966; Brownell et al. 1978; Meier et al. 1984).

Although the presence of myocardial nemaline rods has been reported in cats (Fawcett 1968) and dogs (Munnell and Getty 1968), there is only one description of cardiac involvement in humas, and it bears similarities to the current presentation (Meier et al. 1984). Meier et al. (1984) reported these rods in the quadriceps and myocardium of a young woman who presented with dyspnea. There were no neuromuscular complaints, and electromyography showed no neurogenic or myopathic alteration. As in our case, then, although rods were found both in skeletal and cardiac muscle, the primary symptomatology was cardiac. Furthermore, Meier et al. (1984) also suspected a familial disease given the history of sudden death in their patient's mother and one sister, and they were able to detect rods in trichrome stained sections of the sister's myocardium. Recently, Simpson and Hewlett (1982) urged that testing for nemaline rods become more routine in autopsy investigation of undiagnosed forms of skeletal muscle disease. Of note, they described a patient with nemaline rod myopathy who died from cardiac failure, but they were unable to find myocardial inclusions.

The cardiac inclusions in our two cases had some unusual histologic features not typical of nemaline rods (i.e. smooth borders and hyaline or refractile staining), which we attribute to artifactual and degenerative changes within the myocells. Without ultrastructural confirmation of the Z-band like nature of the myocardial inclusions, we cannot be absolutely certain that they represent the same nemaline rods identified in the skeletal muscle. It seems highly improbable, however, that these patients could have two unrelated inclusion body diseases, one in the heart and another in skeletal muscle. Furthermore, as can be appreciated in Fig. 1 D, the skeletal muscle inclusions, which in many areas had typical nemaline rod-like features, on occasion also had relatively smooth borders and a refractile appearance similar to those in the myocardium.

The accumulating reports of nemaline rod disease stress the need for careful evaluation of cardiac and skeletal muscle in patients with unexplained cardiomyopathy, especially if there is evidence of familial involvement.

Further studies are indicated to determine whether these inclusions are nonspecific, or are indeed related to the pathogenesis of cardiac failure.

*Acknowledgment.* We appreciate the efforts of Ms. Annmarie Piccolo who prepared the manuscript.

## References

Brownell AKW, Gilbert JJ, Shaw DT, Garcia B, Wenkebach GF, Lam AKS (1978) Adult onset nemaline myopathy. Neurology 28: 1306–1309

Conen PE, Murphy EG, Donohue WL (1963) Light and electron microscopic studies of myogranules in a child with hypotonia and muscle weakness. Canad Med Assoc J 89: 983–986

Engel AG (1966) Late-onset rod myopathy (a new syndrome?) light and electron microscopic observations in two cases. Mayo Clin Proc 41: 713–741

Fawcett DW (1968) The sporadic occurrences in cardiac muscle of anomalous Z band exhibiting a periodic structure suggestive of tropomyosin. J Cell Biol 36: 266–270

Hubner G, Grantzon R (1983) Mitochondrial cardiomyopathy with involvement of skeletal muscles. Virchows Arch [Pathol Anat] 399: 115–125

Matsuo T, Tashiro T, Ikeda T, Tsujihata M, Shimomura C (1982) Fatal neonatal nemaline myopathy. Acta Pathol Jpn 32: 907–916

Meier C, Voellmy W, Gertach M, Zimmerman A, Geissbuhler J (1984) Nemaline myopathy appearing in adults as cardiomyopathy. Arch Neurol 41: 443–445

Munnell JK, Getty R (1968) Canine myopathy Z disc alterations resembling those of nemaline myopathy. Lab Invest 19: 303–308

Porte A, Stoeckel M-E, Sacrez A, Batzenschlager A (1980) Unusual familial cardiomyopathy with storage of intermediate filaments in the cardiac muscular cells. Virchows Arch [Pathol Anat] 386: 43–58

Rosai J, Lascano EF (1970) Basophilic (mucoid) degeneration of myocardium. Am J Pathol 61: 99–116

Shafiq SA, Dubowitz V, Peterson H de C, Milhorat AT (1967) Nemaline myopathy: Report of a fatal case, with histochemical and electron miccroscope studies. Brain 90: 817–828

Shy GM, Engel WK, Somers JE, Wanks T (1963) Nemaline myopathy. A new congenital myopathy. Brain 86: 793–810

Simpson R, Hewlett R (1982) Nemaline rod disease, with reference to the routine use of histochemical methods in autopsy investigations. Human Pathol 13: 771–773

Accepted August 5, 1985