Inclusion body myositis

A possible chronic persistent muscle infection by mumps virus[1]

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Inclusion body myositis was diagnosed based on three muscle biopsies on a 24-year-old woman during a 10-month period. She presented with a four-year history of severe painless weakness in her leg muscles that was refractory to both corticosteroid and cytotoxic drugs. Immunostaining for mumps viral antigen was positive for nuclear and cytoplasmic inclusions in skeletal muscle cells.

Index terms: Inclusion bodies, viral • Mumps virus • Myositis

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Inclusion body myositis (IBM) is a distinct clinicopathologic variant of idiopathic inflammatory myopathy that has been recently recognized. It involves both young and elderly adults who, as a rule, do not have associated collagen-vascular or malignant diseases. Inflammation in the muscle is usually mild and serum muscle enzyme levels are often normal or mildly elevated. Unlike other types of idiopathic myositis, IBM is unresponsive to corticosteroid therapy, though the clinical course is more protracted. It is most likely caused by a "slow" mumps virus infection.[1]

Case report

A 24-year-old woman presented in February 1981 with a one-year history of painless weakness in her leg muscles. Climbing stairs and riding a bicycle were difficult. She underwent a muscle biopsy at another hospital in February 1981 and polymyositis was diagnosed. She was treated with 50 mg of prednisone a day, which she took for 6 months without any benefit. In August 1981 she came to the Cleveland Clinic Foundation (CCF).

She had no previous illness except for the usual childhood diseases, including mumps. The family history was noncontributory. Review of systems revealed no skin rashes, arthritis, chest pain, or mucosal lesions. There was full range of motion of all joints and no joint swelling or synovitis was present. She could neither get out of a chair without being supported by her arms, nor stand from a stooped position. Her strength was decreased in proximal muscles more than in distal muscles. Truncal muscles were also weak. Cranial nerves, gait, and sensory examinations were all within normal limits. Despite the slow improvement of creatine phosphokinase (CK) levels (*Table*), her weakness did not improve. In October 1982 she became progressively weaker and prednisone dosage was gradually tapered off. At that time

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Table. Clinical studies and therapeutic course

Date	Study	Creatine phosphokinase (normal <180 U/L)	Aldolase (normal <8 U/L)	Therapy
Feb 81	Bx	?	?	prednisone (50 mg) ↓
Aug 81	Bx, EMG	678	14.2	prednisone (60 mg) ↓ H_2N IV ↓
Sept 81		416	9.3	azathioprine ↓
Oct 81		332	15.3	cytoxan ↓
Jan 82		285	9.7	↓
Feb 82		309	9.9	tapered off
May 82		202	7.7	
Oct 82	Bx, EMG	359	9.6	cytoxan ↓
Dec 82		124	4.5	prednisone (60 mg) ↓
Jan 83		140	3.3	tapered off; cytoxan ↓; MTX ↓
Apr 84		135	2.7	

Bx = muscle biopsy; *EMG* = electromyography; *H_2N* = nitrogen mustard; *MTX* = methotrexate.

she was barely able to lift her neck and legs off the bed. Cytoxan dosage was increased and methotrexate was added. Although the enzyme levels became normal with treatment, the clinical findings did not improve (*Table*). In April 1984 the patient had a marked waddling gait and scapular winging. In addition to marked proximal weakness her feet showed inversion deformity, her fingers were in a flexed position, and she could neither open nor extend her fingers completely. Reflexes were hypoactive. There were no sensory abnormalities. Biopsy and electromyography (EMG) were repeated twice (August 1981 and October 1982) at CCF, and the diagnosis of polymyositis was changed to inclusion body myositis.

Histopathology

On reviewing three muscle biopsy specimens, variable amounts of chronic inflammatory cell infiltrate were seen in the interstitial tissue. The second muscle (left quadriceps) biopsy specimen revealed marked lymphocytic infilitration and moderate fibrosis in the endomysium and severe myofiber loss and atrophy of remaining myofibers. Eosinophilic intranuclear and cytoplasmic inclusions were identified in hematoxylin and eosin (H&E) stained paraffin-embedded sections (*Fig. 1*). Cryosections revealed typical "lined vacuoles" in a few myofibers that were evident in the third biopsy (left vastus lateralis) specimen (*Fig. 2*) but not in the second biopsy specimen. Many angular fibers of denervation atrophy were detected with nonspecific esterase stain. Interstitial blood vessels were free of angiopathic changes, although perivascular lymphocytic infiltration was severe in the second biopsy specimen. As recently reported,[1] immunoperoxidase staining with avidin-biotin complex applied on paraffin sections revealed distinct positivity against mumps virus antigen in both cytoplasmic and intranuclear inclusions in the present case. Mumps-positive intranuclear inclusions were often seen in the center of sarcolemmal nuclei, where a halo could be seen between the central

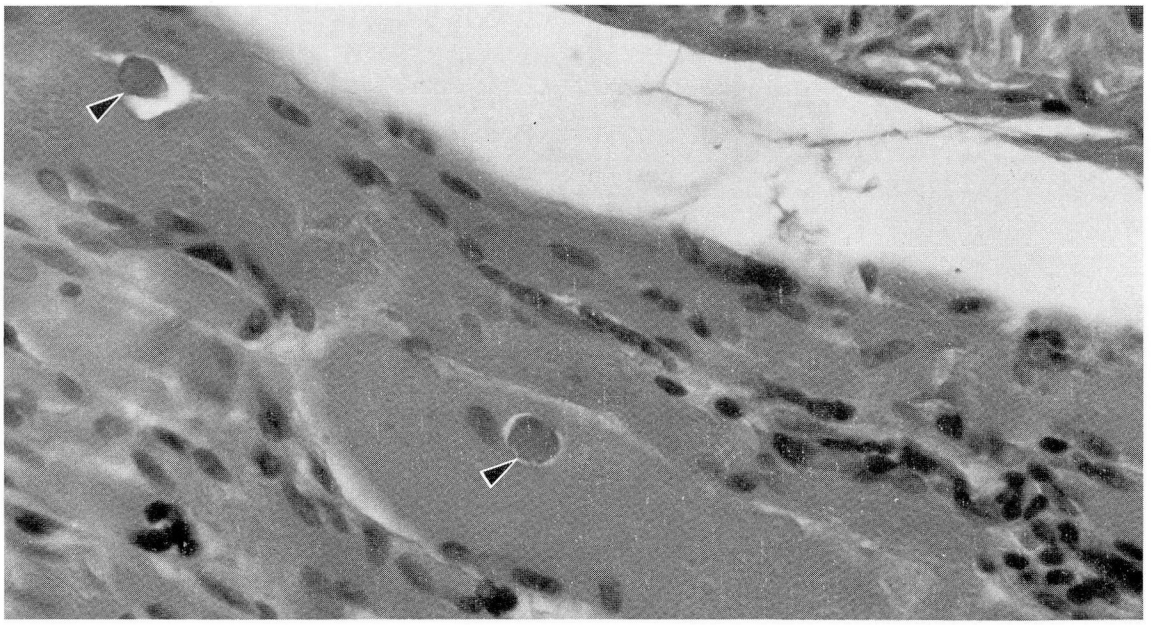

Fig. 1. Mild lymphocytic infiltrate along atrophic myofibers and two eosinophilic inclusions in enlarged nuclei (arrowheads). (H&E stain, ×490)

inclusion and marginated chromatin (*Fig. 3*). Electron microscopy (EM) showed that the vacuoles corresponded to the zones of myelin figures and aggregates of microtubular filaments measuring 15 to 18 nm in the outer diameter, 5 nm in the inner diameter, with longitudinal periodicity of 5 nm. Microtubular filaments were often found in the center of nuclei in which sarcoplasm was free of degenerative change (*Fig. 4*). The intranuclear filamentous inclusions were found in both the second and third biopsy specimens. Higher magnification of the inclusion showed typical microtubular profiles with a somewhat rigid appearance (*Fig. 4* inset).

Discussion

As the term, "inclusion body myositis" implies, the finding of intranuclear and/or intracytoplasmic inclusions in the inflamed muscle specimens is the histopathologic hallmark. However, the inclusions may be difficult to find by routine light microscopy. In the present case they were only identified after ultrastructural studies had revealed their presence. Both intranuclear and cytoplasmic microtubular inclusions were first described in 1967[2] in three muscle biopsy specimens obtained during a 20-month period from a 66-year-old man with chronic polymyositis. Because of the resemblance of the microtubules to paramyxovirus nucleocapsids, a persistent or "slow" paramyxovirus infection was postulated.[3] Similar EM findings were reported in several cases where muscle biopsy was similarly repeated (as done also in the present case) because of skepticism of the original biopsy-based diagnosis of polymyositis, since the patient failed to respond to steroid therapy. In 1971, we reviewed eight IBM cases [4] and documented a propensity of the disease for a more chronic course, less elevated muscle enzyme levels, and absence of associated malignancy or connective tissue disease. Exceptions to this paradigm are two recent IBM cases associated with overt collagen-vascular diseases.[5,6] The term "inclusion body myositis (IBM)" was proposed in 1971 by Yunis and Samaha[7] to separate it from the other types of idiopathic myositis. Adding six of their own cases, Carpenter et al in 1978 reviewed 14 IBM cases and recognized a lack of response to corticosteroid therapy.[8] The presence of the "lined vacuoles" was emphasized as the diagnostic landmark. The disease was considered to occur only in the elderly. However, Eisen et al[9] reviewed 34 reported IBM cases and identified well-delineated, bimodal age distribution with onset in the second and sixth decades. Affected women tended to be young and to have higher serum CK levels, as exemplified in our case. The possibility of a con-

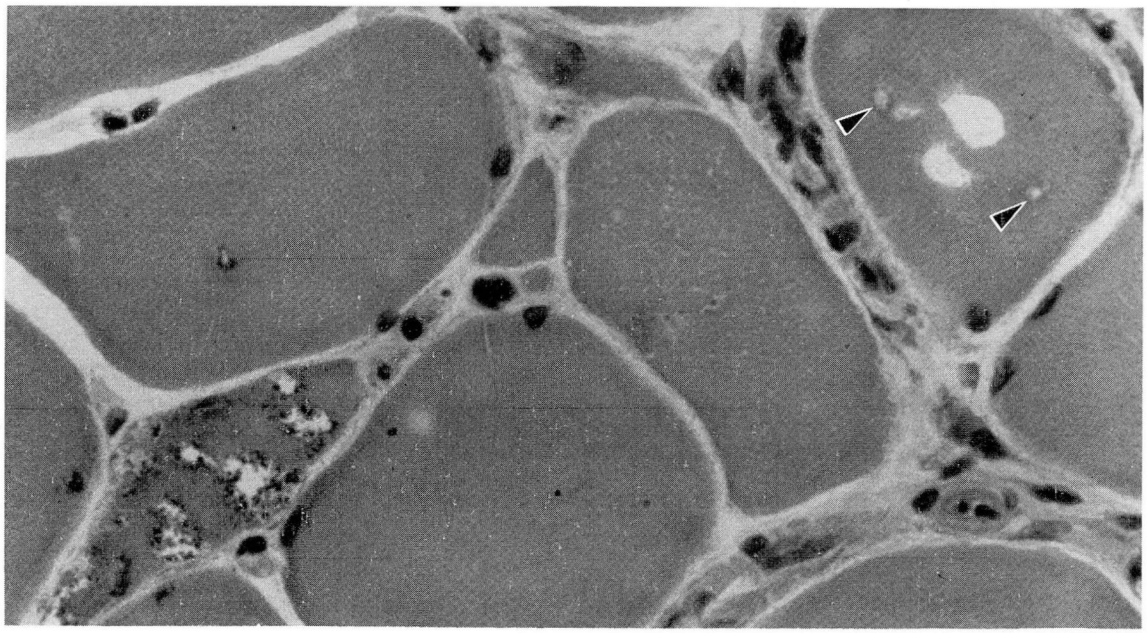

Fig. 2. Transversely cut cryosections of myofibers showing typical "lined vacuoles" at the left lower corner and smooth vacuoles in the right upper corner with vacuolated nuclei (arrowheads). Note several small angular fibers. (H&E stain, ×490)

comitant peripheral nerve involvement was first suggested by Jerusalem et al in 1972[10] and later shown to be a relatively common complication.[9]

The present case then typifies the clinical course of this disease. As underscored in the case history, the disease is characterized by a protracted painless muscle disease involving distal and proximal muscles, with loss of tendon reflexes. In contrast to other inflammatory myopathies: (*a*) the serum CK levels were only mildly elevated; (*b*) distal muscle weakness with atrophy was a prominent feature; (*c*) neuropathic features were present electrophysiologically and/or histopathologically; (*d*) collagen-vascular disease or malignancy was not present; and (*e*) the patient failed to respond to high-dose corticosteroid and cytotoxic therapy.

EMG findings were variable and both myopathic and neurogenic changes have been described. In most patients, needle EMG showed numerous fibrillation potentials and reduced recruitment. Two types of polyphasic motor unit patterns, one with long duration, high amplitude and the other with short or moderate duration, have often been described. The former pattern was interpreted as "neurogenic" and, indeed, some patients showed slow nerve conduction velocities.[9,11]

In addition to histopathologic features of polymyositis (inflammation, regeneration, and myonecrosis), if any of the following are found in muscle specimens, IBM should be suspected: (1) intracytoplasmic and/or intranuclear inclusions, (2) "lined vacuoles", (3) "ragged-red" fibers, and (4) clusters of atrophic fibers. Large intranuclear or intracytoplasmic eosinophilic inclusions, which tend to have a distinct halo around them, can be detected in routinely prepared paraffin-embedded sections. However, in cryosections, the halo is absent and detection is difficult. In cryosections, "lined vacuoles" are more characteristic and readily discernible than inclusions. The vacuoles are "plastered" along the vacuolar walls with fine basophilic granules seen with H&E, or deep purple granules with the Gomori trichrome stain. "Ragged-red" fibers, indicative of abnormal mitochondrial accumulation, tend to increase in number. In keeping with EMG findings, occasional clusters of atrophic fibers suggestive of denervation can be found. EM demonstation of the inclusions consisting of microtubular filaments (15–18 nm width, with 4–6 nm central hole) is essential for establishing the diagnosis of IBM. The microtubular filaments appear rigid and straight. Their rippled outlines in both cross and longitudinal sections and periodic transverse

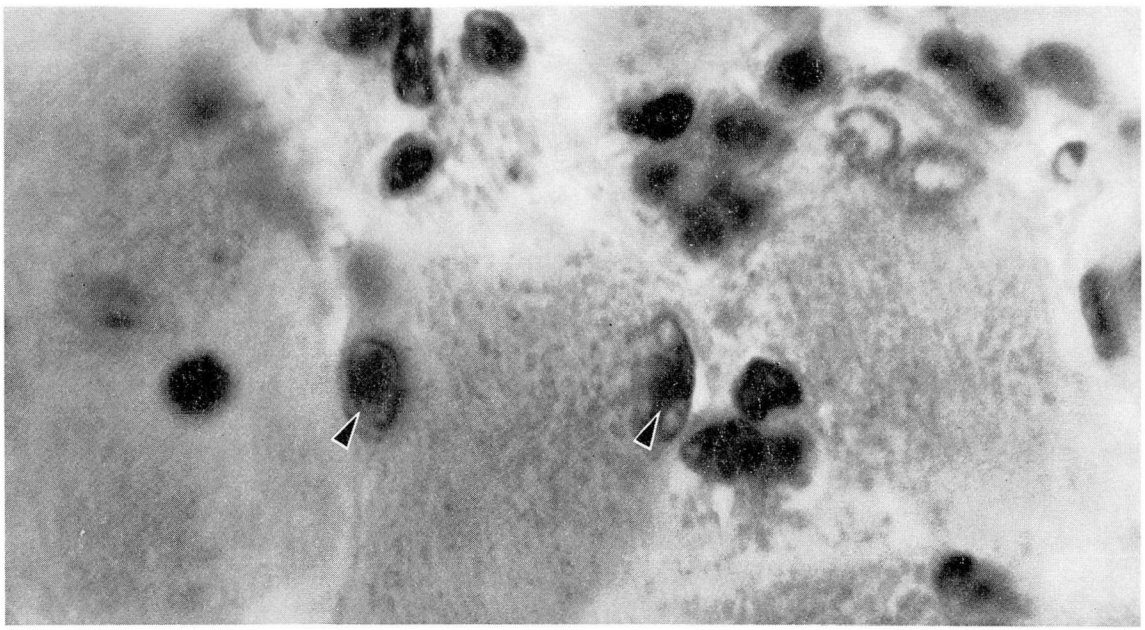

Fig. 3. Immunoperoxidase stain with avidin-biotin complex for mumps virus antigen applied on paraffin section, showing two positive intranuclear inclusions with halos (arrowheads) in the myofiber free of sarcoplasmic degeneration. (Hematoxylin stain, ×780)

striation suggest a helical structure. The dimensions and appearance of the filaments conform to those of the nucleocapsid of paramyxovirus (18 nm width, 4 nm central hole, and 4 nm periodicity).

Histopathologic diagnosis of IBM is often elusive, as exemplified in the present case. Lined vacuoles were absent in the second biopsy specimen. Yet EM study demonstrated the intranuclear microtubular inclusions (*Fig. 4*). If the microtubular filaments represent nucleocapsids of a paramyxovirus, they may represent those of a defective virus incapable of growing in conventional cell lines, since viral isolation has been previously attempted by many in vain. Recently we have applied an immunoperoxidase technique with avidin-biotin complex (ABC) on biopsy specimens from six EM-proved IBM cases, including this case, for screening eight different paramyxoviruses or myxoviruses (influenza A,B, parainfluenza 1, 2, 3, respiratory syncytial, measles, and mumps). Mumps virus antigen alone was constantly demonstrated in all six IBM cases and it was visualized in both paraffin and frozen sections.[1] In four of six patients where the inquiry was made, all had a past history of mumps infection. Hence this preliminary study strongly indicates that IBM is caused by a chronic persistent infection by a defective mumps virus. Four frozen specimens from those six cases (including the present case) were sent to Dr. Duard Walker in the Department of Microbiology at the University of Wisconsin Medical School, Madison, Wisconsin for mumps virus isolation. The attempts with various modifications for viral culture to date have been unsuccessful.

IBM is refractory to steroids or cytotoxic agents and a specific therapeutic approach aimed at the putative causative agent, mumps virus, must be contemplated. Since 1967, when mumps vaccine was licensed, over 65 million doses of mumps vaccine have been distributed in the U.S. In 1984 the CDC reported a 90% or greater decline from 1968 in the reported cases of mumps. The trend for disappearing active mumps infection does not necessarily preclude the possibility of increasing permissive mumps infection. Since some of our IBM patients had had mumps infection in the past, further mumps immunization may not be of any help. One IBM patient was reported to have clinical improvement after total-body irradiation.[12]

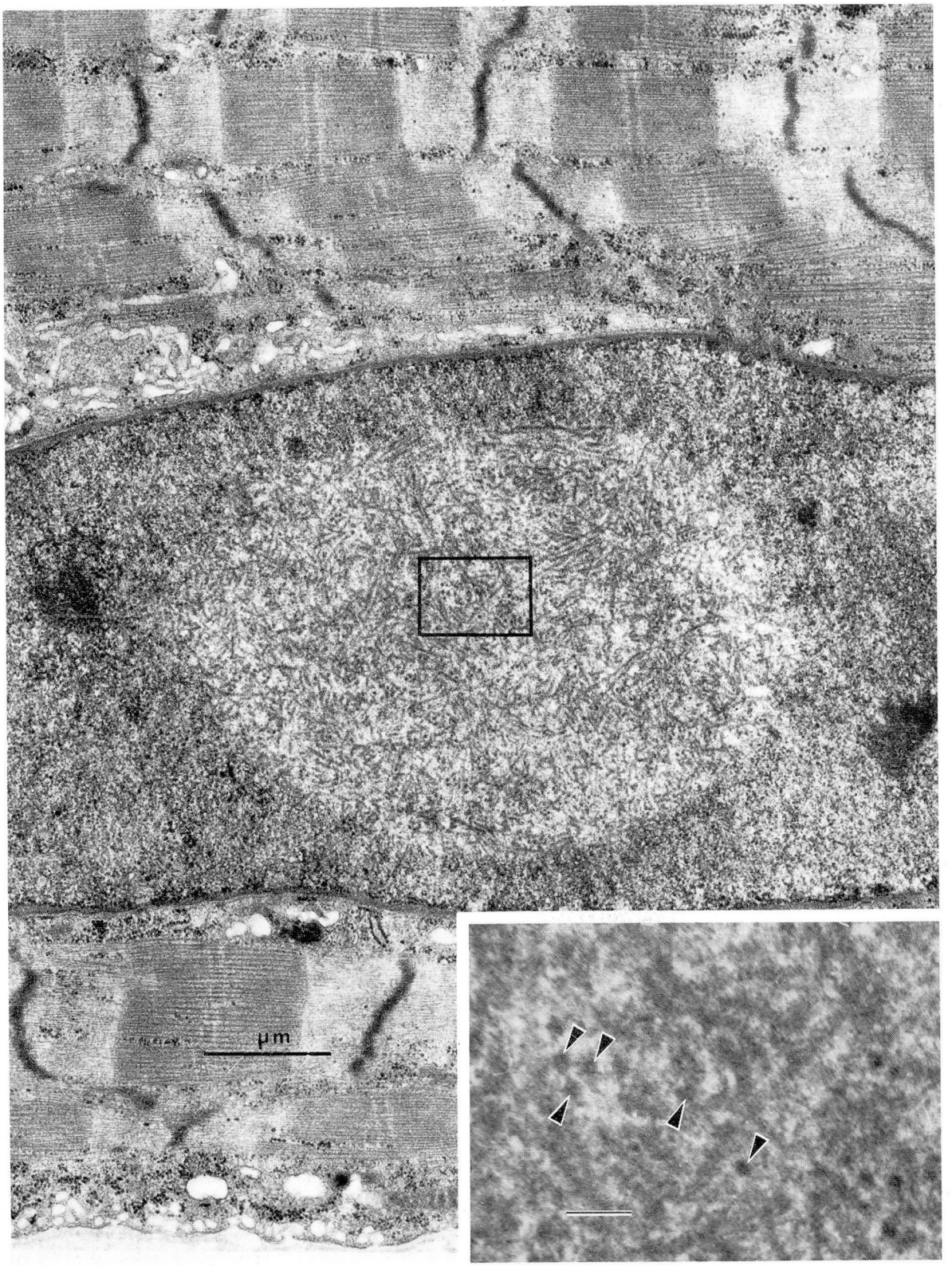

Fig. 4. A round area of intranuclear filamentous inclusion in otherwise normal-appearing sarcolemmal nucleus. (×21,800) Inset: Higher magnification of the squared area showing microtubular profiles with a central hole 5 nm in diameter (arrowheads) (×109,000) (with a 100-nm bar).

Acknowledgment

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References

1. Chou SM, Mizuno Y. Mumps virus antigen in inclusion body myositis (IBM). Neurol 1985;**35** (Suppl 1):204. J. Neuropathol Exp Neurol 1985;**44**:361. (abstr)
2. Chou SM. Myxovirus-like structures in a case of human chronic polymyositis. Science 1967;**158**:1453–1455.
3. Chou SM. Myxovirus-like structures and accompanying nuclear changes in chronic polymyositis. Arch Pathol 1968;**86**:649–658.
4. Chou SM. Prospects of viral etiology in polymyositis. [In] Kakulus BA, ed. Proceedings. Second International Congress in Muscle Diseases. Amsterdam, Exerpta Medica, 1972, pp 17–28.
5. Chad D, Good P, Adelman L, Bradley WG, Mills J. Inclusion body myositis associated with Sjögren's syndrome. Arch Neurol 1982;**39**:186–188.
6. Lane R, Fulthorpe JJ, Hudgson P. Inclusion body myositis: A case with associated collagen vascular disease responding to treatment. J Neurol Neuros Psych 1985;**48**:270–273.
7. Yunis EJ, Samaha FJ. Inclusion body myositis. Lab Invest 1971;**25**:240–248.
8. Carpenter S, Karpati G, Heller I, Eisen A. Inclusion body myositis: A distinct variety of idiopathic inflammatory myopathy. Neurol (NY) 1978;**28**:8–17.
9. Eisen A, Berry K, Gibson G. Inclusion body myositis (IBM): Myopathy or neuropathy? Neurol (Cleveland) 1983;**33**:1109–1114.
10. Jerusalem F, Baumgartner G, Wyler R. Virus-ähnliche Einschlüsse bei chronischen neuro-muskulmuskulären Prozessen. Elekronenmikroskopische Biopsiebefunde von 2 Fällen. Arch Psychiatr Nervenkr 1972;**215**:148–166.
11. Danon MJ, Reyes MG, Perurena OH, Masdeu JC, Manaligod JR. Inclusion body myositis: A corticosteroid-resistant idiopathic inflammatory myopathy. Arch Neurol 1982;**39**:760–764.
12. Kelly JJ, Madoc-Jones H, Adelman LR, Munsat TL. Treatment of refractory polymyositis with total body irradiation. Neurol 1984;**34** (Suppl):80. (abstr).

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