Inclusion body myositis:
Explanation for poor response to immunosuppressive therapy

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Article abstract—We treated eight patients who had inclusion body myositis (IBM) with oral prednisone therapy, and we performed muscle biopsies before and after treatment. We documented the patients' clinical response to therapy and changes in serum CK. Although the serum CK level fell, muscle strength worsened after prednisone treatment. In addition, while inflammation decreased in the muscle biopsy specimens, the number of vacuolated and amyloid-positive fibers increased after oral prednisone therapy. These observations indicate that the inflammatory response in IBM may play a secondary role in the pathogenesis of IBM. The unique findings of intracellular amyloid deposits and rimmed vacuoles distinguishing IBM from other inflammatory myopathies, and recognition that suppression of inflammation has no effect on the clinical course, suggest that IBM may represent a degenerative muscle disorder.

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The three major categories of inflammatory myopathy are polymyositis, dermatomyositis, and inclusion body myositis (IBM), with the latter accounting for at least 30% of inflammatory myopathy cases referred to a tertiary care center.[1] The histologic constellation of IBM consists of endomysial inflammation, rimmed vacuoles in muscle fibers, and the identification of 15- to 18-nm filaments usually found in the cytoplasm and less often in the nucleus. Mendell et al[2] identified intracellular (mostly cytoplasmic but also intranuclear) amyloid deposits in muscle fibers in IBM patients; apple-green birefringent deposits are visualized with polarization microscopy of Congo red-stained muscle of IBM patients.

A notable feature of IBM is the clinical progression of muscle weakness despite immunosuppressive therapy at doses adequate to treat dermatomyositis and polymyositis. These observations raise questions about the role of mononuclear cell invasion of muscle fibers in the relentless course of IBM. In eight patients with IBM treated for 6 to 24 months (table), we compared findings on repeat muscle biopsies with the clinical response and serum CK levels.

Methods. Eight patients fulfilled clinical and histologic criteria for IBM.[1] All biopsies showed characteristic Congo red deposits typical of amyloid in the muscle biopsy specimens. Following diagnosis, all patients were treated with single, daily-dose prednisone 100 mg/day for 4 weeks and then switched to alternate-day doses of 100 mg for at least 6 months (patients 1 and 8 for 24 months; patients 2, 3, and 6 for 12 months; patient 4 for 11 months; patient 7 for 8 months; patient 5 for 6 months). After this period of oral prednisone therapy, each patient was asked to undergo a repeat muscle biopsy and gave informed consent. The second biopsy specimen was obtained from the same muscle group as the first specimen but in the contralateral extremity. Patients were not receiving other immunosuppressive therapies during this period.

For all patients the average muscle score (AMS) was calculated[3] using a modified Medical Research Council scale expanded to a 10-point system. In addition, functional disability scores were obtained: 0 = no functional problems; 1 = minor symptoms (capable of running); 2 = able to walk 30 feet with assistance but unable to run; 3 = able to walk 30 feet with assistance (walker or cane); 4 = able to walk less than 30 feet with assistance; 5 = wheelchair bound. AMS, functional score, and serum CK levels were obtained before and after prednisone therapy.

In pre- and post-treatment muscle biopsies, the area of each was determined in a hematoxylin and eosin (H-E)-stained section using a morphometric system previously described.[2] A serial section was stained with Congo red. The total number of non-necrotic muscle fibers invaded by mononuclear cells was counted in the H-E section to ensure inclusion of all invaded muscle fibers irrespective of inflammatory cell type. The number of muscle fibers harboring vacuoles was also quantified using a modified trichrome stain, and in Congo red-stained sections, viewed under polarized light, a count of the total number of fibers demonstrating amyloid deposits was determined. Counts were expressed as the number of fibers/mm^2 tissue. The differences between the counts from the first and second muscle biopsies were expressed as an increase (positive number) or decrease (negative number) per year (table).

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Table. Clinical and histologic findings before and after prednisone

Pt no.	Age/Sex	Average muscle score		Functional score		Creatine kinase (IU/l)		Cell infiltration (no. change/yr)‡	Vacuolated fibers (no. change/yr)‡	Amyloid-positive fibers (no. change/yr)‡
		Pre*	Post†	Pre*	Post†	Pre*	Post†			
1	74/F	8.7	7.2	2	2	1,384	347	–1.72	+0.60	+0.04
2	63/F	6.3	5.8	2	2	400	67	–0.95	+1.78	+1.74
3	77/F	7.7	6.7	2	2	708	200	–2.23	–0.60	–0.25
4	70/M	7.6	7.4	2	2	405	398	–6.80	+4.98	+0.82
5	74/M	7.0	6.0	2	2	674	46	–0.19	+0.59	+0.51
6	73/M	6.7	5.4	3	4	700	170	–2.77	+23.78	+8.67
7	72/M	7.7	6.9	3	3	386	243	–3.78	+3.80	+1.39
8	47/F	7.6	6.7	3	3	1,896	106	–1.86	+0.41	+0.13
Mean		7.3	6.4			819	197	–2.53	+4.41	+1.63
± SD		0.78	0.73			542	127	2.03	8.04	2.92

* Pre-prednisone.
† Post-prednisone.
‡ Increase (positive number) or decrease (negative number), derived from number of fibers per mm^2 tissue of pre- and post-treatment muscle biopsies.

Results. Following prednisone therapy, serum CK levels declined in all eight patients; four fell into the normal range. No improvement was noted in AMS or functional disability score. In fact, AMS deteriorated in all eight patients and disability score deteriorated in one patient (table).

In all post-treatment muscle biopsy specimens, the number of non-necrotic muscle fibers with mononuclear cell invasion decreased (table). In contrast, the number of vacuolated and amyloid-positive fibers increased in all but one case (patient 3).

Discussion. The results of this study demonstrate paradoxical observations. Despite suppression of mononuclear cell invasion of non-necrotic muscle fibers and decreased serum CK levels, muscle strength continued to deteriorate while patients were treated with prednisone therapy. The progressive muscle weakness was associated with an increased number of vacuolated muscle fibers and amyloid-positive fibers. Although the histologic changes in IBM are a multifocal process,[4] and while the second biopsy was done in a muscle from the contralateral limb, the findings following prednisone therapy clearly did not follow a random distribution. Cell infiltration declined in every prednisone-treated patient, while vacuoles and amyloid-positive fibers increased in all but one patient. These findings suggest that the inflammatory response is not solely accountable for the relentless course, because suppression of inflammation will not halt the progression of disease. An untreated control group for comparison or further documentation of the natural history would be necessary to define the degree of disability induced by inflammation alone.

Despite limitations, these findings emphasize the potential importance of the vacuolated fibers and amyloidogenic material in the underlying pathogenesis of muscle weakness. Some investigators have attempted to establish analogies between IBM and Alzheimer's disease (AD) because of the amyloid deposits. Askanas et al[5] have shown that the amyloidogenic protein deposited in IBM is beta-amyloid. In addition, the N- and C-terminal epitopes of amyloid precursor protein, ubiquitin, antichymotrypsin, apolipoprotein E, and hyperphosphorylated tau protein accumulate within the vacuolated muscle fibers of IBM.[5-9] These same proteins are present within the senile plaques and neurofibrillary tangles in the brains of AD patients.[10] Co-localization studies for the presence of these proteins by electron microscopy has demonstrated that tau protein and ubiquitin are present on bundles of cytoplasmic tubulofilaments (15 to 18 nm) while beta-amyloid protein is exclusively localized to 6- to 10-nm filaments.[5,7] The pathogenic mechanisms that produce the accumulation of this aberrant material in AD and IBM remain unknown. The potential similarities are, however, of interest since both disorders are relentlessly progressive. In addition, while most cases of AD and IBM are sporadic, autosomal dominant kindreds occur in both diseases.[11-13] Rimmed vacuoles, 15- to 18-nm tubulofilaments, and amyloid deposition are not specific for IBM and can be demonstrated in noninflammatory myopathies such as oculopharyngeal dystrophy[14] and some forms of distal myopathy.[15]

It remains difficult to account for the inflammatory response in IBM, which can reach rather florid proportions in some patients. Could it be secondary to the amyloidogenic material? Evidence suggests a lack of relationship, since a common observation is the failure to identify mononuclear cells invading amyloid-positive fibers. On the other hand, inflammation may be seen in muscular dystrophies such as Duchenne muscular dystrophy,[16] facioscapulohumeral dystrophy,[17] and oculopharyngeal dystrophy,[18] in which the inflammatory response represents a secondary phenomenon. A localized inflammatory reaction can also occur in the brain in AD.[10]

Despite the lack of current understanding of IBM, a series of recent observations,[2,5-9,19] including those reported here, continues to emphasize the distinction among IBM, polymyositis, and dermatomyositis. This study again emphasizes that immunosuppressive therapy, in this case prednisone, is not clinically effective in the treatment of IBM. In this regard, we recently reported that IBM does not respond to IV immunoglobulin,[19] although an earlier smaller series suggested a possible benefit.[20] On the other hand, IV immunoglobulin appears to be an effective therapy for dermatomyositis.[21] The lack of response to immunosuppressive therapy in IBM, along with our histologic data and that of others,[5-9] suggests that progression of weakness in IBM cannot be explained on the basis of inflammation. More studies are needed to elucidate the pathogenesis of this distinctive myopathic disorder.

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