Idiopathic inflammatory myopathies: inclusion-body myositis, polymyositis, and dermatomyositis

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In this review, the main emphasis is on new advances concerning sporadic inclusion-body myositis and hereditary inclusion-body myopathy. Polymyositis and dermatomyositis are reviewed briefly. Hypotheses are presented regarding the possible cause and significance of abnormally accumulated -amyloid protein, two other epitopes of -amyloid precursor protein, hyperphosphorylated 't, a.1-antichymotrypsin, ubiquitin, and prion protein in sporadic inclusion-body myositis and hereditary inclusion-body myopathy. Because most of those proteins are also accumulated at the neuromuscular junction, "junctionalization" of other muscle fiber nuclei is a possibility. Attention is given to the fact that vacuolated muscle fibers in hereditary inclusion-body myopathy may represent early changes because they are virtually free of congophilic amyloid deposit but, like sporadic inclusion-body myositis, contain large accumulations of 13-amyloid protein and prion.

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The idiopathic inflammatory myopathies are a group of diseases of unknown pathogenesis that are characterized by mononuclear cell infiltration in muscle. They exclude diseases of bacterial, viral, and other known causes. This review also excludes the inflammatory myopathies of sarcoidosis and HIV infection. It concentrates on inclusion-body myositis (IBM) and briefly reviews adult polymyositis and dermatomyositis. Recent in-depth reviews of polymyositis and dermatomyositis are recommended [1,2,3.. J.

Sporadic inclusion-body myositis and hereditary inclusion-body myopathy

Sporadic inclusion-body myositis

Sporadic inclusion-body myositis (s-lBM) is the most common muscle disease beginning in patients 50 years of age and older [2,4•,S,6•]. Predominantly in men, distal and proximal muscle weakness is present. There is a characteristic thinning of the forearms, which is associated with weakness of the finger extensors, flexors, or both, and prominent involvement of the quadriceps. The slowly progressive course usually leads to severe disability and eventually to respiratory muscle weakness. Dysphagia is fairly common; it can appear during the muscle weakness or precede it [7]. In older patients with dysphagia, IBM should be in the differential diagnosis.

Even though patients often show poor or no response to prednisone and other immunosuppressive treatments, in our experience occasional patients have significant improvement with prednisone (20 to 60 **mg** as a single dose on alternate days), oral cyclophosphamide (2 mg/kg/d) or total-body irradiation (Engel and Askanas, Unpublished data). This benefit can persist for 6 months to 5 years (and sometimes longer), but normal strength is not restored. Similar benefit was recently reported by others [8,9], but drug doses and duration of improvement were not stated in one report [9]. Treatment with intravenous immunoglobulin was reported to be beneficial in three of four s-IBM patients [10]; however, this finding was not confirmed by another trial in seven patients [11].

The light microscopic pathologic features of s-IBM include degrees of mononuclear cell inflammation that vary from abundant in the early stages to little or none in the later stages; muscle fibers with one or several irregular vacuoles that are usually red rimmed (on Engel-Gomori trichrome staining [12]), which are more common in the middle and later stages; and atrophic angu-

Abbreviations

A1}-P-amyloid protein; PAPP-p-amyloid precursor protein; h-lBM-hereditary inclusion-body myopathy; IBM-inclusion-body myositis; mRNA-messenger RNA; s-lBM-sporadic inclusion-body myositis.

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lar muscle fibers, which are histochemically dark with panesterase and NADH-tetrazolium reductase reactions and considered to be indicative of a denervation component [4•]. The inflammatory cells are similar to those in polymyositis, being mainly CDS+ cytotoxic T cells (3.. ,13). In both diseases, macrophages comprise approximately 20% to 30%, of the cells surrounding or invading nonnecrotic muscle fibers; within necrotic fibers, they make up 80% of the invading cells 113). Because red-rimmed vacuoles are sometimes present in only a few muscle fibers and can be very small, s-**IBM,** especially in its early stages, can be difficult to distinguish from polymyositis by routine histochemistry. In general, s-IBM is probably underdiagnosed, more so in some countries 114). To help differentiate s-IBM from polymyositis by light microscopy of fresh-frozen sections, we suggest 1) Engel-Gomori trichrome staining for red-rimmed vacuoles; 2) fluorescence-enhanced Congo red 115..) or crystal-violet staining for small bits of amyloid within some vacuolated fibers; 3) alkaline phosphatase staining for connective tissue (typically negative or low in s-IBM but usually prominent in polymyositis) (Askanas and Engel, Unpublished **data);** and 4) immunocytochemical staining for ubiquitin, for which commercial antibody can be used 116).

The ultrastructural diagnostic criterion for s-IBM is the presence of cytoplasmic "twisted tubulofilaments" of 15 to 21 nm in external diameter 14•]; they are, in fact, paired helical filaments with a twist repeat at 45 to 55 nm 117..). IBM muscle paired helical filaments closely resemble the paired helical filaments of Alzheimer's disease brain 117..). IBM vacuolated muscle fibers also contain clusters of 6- to 10-nm amyloid-like fibrils 118,19••], fine flocculomembranous material, and amorphous material 118,19.. 1. Myelin-like whorls and various other lysosomal and cellular debris are also present.

Hereditary inclusion-body myopathy

Hereditary inclusion-body myopathy (h-IBM) is included in this review because it has striking morphochemical phenotype similarities to s-IBM, as described later. h-IBM is inherited either as an autosomal recessive or an autosomal dominant trait 14•). The genetic locus (or loci) is not known. The onset is usually at a younger age than that of s-IBM *(eg,* at 15 to 40 years of age). Patients with h-IBM have progressive proximal and distal muscle weakness. As in s-IBM, the finger flexors and extensors are typically involved, but in the recessive form of h-IBM, unlike in s-IBM, the quadriceps are typically spared. As in s-IBM, muscle h-IBM fibers have typical irregular vacuoles (which are often not as red rimmed as s-IBM fibers) and paired helical filaments. Our patients with autosomal recessive h-IBM lack mononuclear inflammation in the biopsy specimen by routine histochemistry (in some patients with autosomal dominant h-IBM, a degree of inflammation has been reported by others 120,21), but we have not seen this characteristic in our few cases). To emphasize the typical lack of inflammation, we introduced the term *hereditary inclusion-body myopathy* 14•).

Because no strict diagnostic criteria exist for h-IBM, several syndromes with different clinical presentations are sometimes included. One distinct subgroup consists of patients with autosomal recessive inheritance, many of whom are Persian (Iranian) Jews with characteristic sparing of the quadriceps muscle 117.. ,22,23.. l; they have frequent consanguinity, sometimes causing a "pseudodominant" pattern, *eg,* when affected children issue from an affected person married to a cousin who is a carrier (Engel and Askanas, Unpublished data). A Tunisian autosomal recessive kindred with a quadriceps-sparing neuromuscular disorder and symptomatic leukoencephalopathy has been reported 124). Another kindred has asymptomatic periventricular leukoencephalopathy but not quadriceps-sparing 1251. Other patients with autosomal recessive inheritance and different clinical manifestations126) have also been considered to have an IBM-like disorder. None of the patients with autosomal recessive inheritance have inflammation in their muscle biopsy specimens 117.. ,24-26). Autosomal dominant h-IBM in a large pedigree was reported recently 121), and other families are unpublished (Engel, Unpublished data; Heller *et al.,* Unpublished data).

Unusual aspects of sporadic inclusion-body myositis and hereditary inclusion-body myopathy pathology

Intracellular amyloid deposits

Amyloid denotes the physical configuration of any protein aggregated in P-pleated sheets that stains with Congo red *(ie,* is Congophilic) and is metachromatically pink with crystal-violet. A number of different proteins, including the P-amyloid protein (AP) part of P-amyloid precursor protein (PAPP), have the propensity to self-aggregate in this way. Congo red-positive amyloid was demonstrated in vacuolated IBM muscle fibers by Mendell *et al.* 127), and we confirmed this finding with thioflavin S and crystal-violet staining 128,29). Our new method of fluorescence-enhanced Congo red positivity 115.. 1, which enables identification of even very tiny amyloid deposits, reveals amyloid in virtually 100% of s-IBM vacuolated fibers 115.. ,17..). However, fluorescence-enhanced Congo red positivity of the vacuolated fibers occurs in only 30% of our patients with autosomal recessive h-IBM (and in them, in only 30% to 400/4 of their vacuolated fibers) 14•,17••].

Unresolved questions about the Congophilic amyloid in s-IBM relate to its chemical nature and origin, the type of subcellular structure containing it, and its initial location in the muscle fiber. In IBM muscle fiber, the Congophilic amyloid might or might not be partially due to API28,29), which is a 39- to 42-residue polypeptide part of PAPP 1301. (AP is the major component of amyloid fibrils in blood vessels and senile plaques in the brain of Alzheimer's disease, Down's syndrome, Dutch hereditary cerebrovascular amyloido-

sis, and those of very advanced age 130,311; in these conditions, abnormal accumulation of AP is considered to be partially due to increased generation of PAPP and partly to abnormal processing of it 130,311.) Because injected ubiquitin was reported to induce amyloidogenesis 1321, it is of interest whether the increased ubiquitin in s-lBM and h-lBM muscle fibers 1331 can enhance amyloid deposits there.

Whereas some of the Congophilic amyloid deposits are located deep within the muscle fiber, others are subjacent to the plasmalemma, and some appear to have come out of the muscle fiber 14•). None of our 12 patients with several other vacuolar myopathies, including acid-maltase deficiency, hypokalemic periodic paralysis, and undefined types, had Congophilic amyloid deposits. As in s-lBM, abnormal muscle fibers in some of these disorders can have increased acid phosphatase staining indicative of increased lysosomal activity, and this increased staining is very prominent in acid-maltase deficiency. Because such biopsy specimens do not have Congophilic amyloid, it is unlikely that the amyloid deposits in s-lBM result from a nonspecific disturbance of lysosomal function. In our experience to date, the only non-IBM muscle disorder with intramyofiber Congophilia is oculopharyngeal muscular dystrophy, in which we found it in two of two patients (Unpublished data). Abnormal muscle fibers in oculopharyngeal muscular dystrophy can also have increased ubiquitin deposition 1331. Whether intramyofiber Congophilia will be convincingly demonstrated in any other muscle disease remains to be seen.

Abnormal accumulation of characteristic Alzheimer proteins and prion

Within the vacuolated muscle fibers of s-lBM and h-IBM, we have identified abnormal accumulations of prion protein [34..] and several proteins typically accumulated in the brains of patients with Alzheimer's disease, *ie,* AP 128,291, N- and C-terminal epitopes of PAPP [19.. l, cx.i-antichymotrypsin 135•1, hyperphosphorylated tll 7.. 1, apolipoprotein E 136•1, fibroblast growth factor (371, and ubiquitin {10,331. The accumulation of ubiquitin [38,391 and PAPP 138,40) in S-IBM fibers has been confirmed by others. Nicotinic acetykholine receptor, its 43-kD associated protein (41), and transforming growth factor-P (42) are also abnormally accumulated in IBM vacuolated muscle fibers. The total ensemble of proteins that we have found to be accumulated excessively in s-IBM and h-IBM muscle fibers appears to be unique for these diseases in our experience to date. We cannot be certain whether this will remain true as more muscle diseases are studied in similar detail. In oculopharyngeal muscular dystrophy, two of the proteins are accumulated, ubiquitin 133,381 and PAPP 1401 (Askanas *et al.,* Unpublished data).

Levels of PAPP messenger RNA, (mRNA) encoding PAPP containing the Kunitz-type proteinase inhibitor sequence 143.. l, and prion protein messenger RNA (Sarkozi *et al.,* Unpublished data) are also increased within vacuolated s-IBM and h-IBM muscle fibers, indicating that the abnormal accumulation of the corresponding proteins is caused, at least partly, by locally increased generation.

In both s-IBM and h-IBM vacuolated muscle fibers, prion, PAPP, apolipoprotein E, ubiquitin, fibroblast growth factor, transforming growth factor-P, and **a.1-an**tichymotrypsin are abundantly present. In h-IBM, hyperphosphorylated t is present in only 24% of the vacuolated muscle fibers that are immunoreactive with the other excessive proteins {17..). Thus, paucity of both Congophilic amyloid and hyperphosphorylated t in the h-IBM vacuolated muscle fibers is a subtle quantitative distinction from s-IBM. In our h-IBM patients, double-fluorescence studies revealed some vacuolated muscle fibers that were AP immunoreactive but Congo red negative 117.. ,291; we conclude that in these fibers, AP is not in P-pleated sheets (as is the case with AP in Congo red negative diffuse plaques of Alzheimer's brain disease 144).) Perhaps these h-IBM fibers are in an earlier stage of the pathologic process (as was also suggested for Alzheimer's diffuse plaques). Two other speculations are 1) that when the t epitope known to be in IBM paired helical filaments [17••] is antigenically intact and in a configuration that is immunohistochemically demonstrable with the antibody, it might be at least partly responsible for Congophilia and 2) that AP accumulation in the p-pleated sheet configuration might lead to induction of the hyperphosphorylated t antigenic material.

Ultrastructural localizations

Gold immunolocalization of the characteristic Alzheimer proteins and prion protein in vacuolated IBM muscle fibers (Table 1) strikingly resembles their localization in abnormal brain. First, as in **Alzheimer's** brain, AP is immunolocalized to 6- to 10-nm amyloid-like fibrils, amorphous structures, and flocculomembranous material, in each of which it closely colocalizes with ubiquitin; C- and N-terminal epitopes of PAPP are present on amorphous structures and flocculomembranous material but not on the 6- to 10-nm fibrils (51. However, the intracellular paired helical filaments, in both IBM muscle and brain, do not contain either PAPP or AP immunoreactivity [1<)-•,29,45). Second, hyperphosphorylated t is present only in paiJ'ed helical filaments It7••], and third, apolipoprotein E is present mainly on paired helical filaments (36•).

Prion protein is localized to paired helical filaments flocculomembranous and amorphous structures, and the 6- and 10-nm amyloid-like fibrils (where it colocalizes with Al3) 134-J. Moreover, nicotinic acetylcholine receptor is localized to paired helical filaments arid to paired helical filaments and to flocculomembranous and amorphous structures, but the 43-kD protein is strongly localized to paired helical filaments only [4l'] (Table 1).

Table 1. Subcellular localization of P-amyloid precursor protein epitopes, ubiquitin, prion, hyperphosphorylated t, n-acetyld1oline receptor, and 43-kD **protein** in inclusion-body myositis muscle

Structure	13-Amyloid protein	N-terminal j3APP epitope	C-terminal j3APP epitope	Ubiquitin	Prion	Hyperphos-phorylated t	Apolipoprotein **E**	Nicotinic acetylcholine receptor	43-kD protein
Paired helical filaments	-	-	-	+	+	+	+	+	+
6- to 10-nm amyloid-like fibrils	+	-	-	+	+	-	+/-	-	-
Amorphous structures	+	+	+	+	+	-	+/-	+/-	-
Floculomembranous material	+	+	+	+	+	-	+/-	+/-	-

(+) Denotes presence of the element and (-) denotes absence.
IIAPP-P-amyloid precursor protein.

Tissue culture of hereditary inclusion-body myopathy muscle

When autosomal recessive Persian Jewish h-IBM muscle is cultured aneurally, it expresses a partial IBM phenotype, in the form of vacuoles and increased PAPP accumulation (Askanas and Mcferrin, Unpublished data). When innervated by motor neurons from cocultured fetal rat spinal cord to produce rather well differentiated muscle fibers, h-IBM fibers from two other patients showed even more of the IBM phenotype, *ie,* paired helical filaments [26,461. Because these characteristic features have been reproduced in cultured h-IBM muscle, this culture model can provide genetically and morphologically abnormal living tissue that is readily accessible for a wide range of molecular studies, including gene transfer (to date, we have transferred three different genes in an adenovirus vector to our cultured human muscle fibers).

Speculations on the pathogenesis

Considerations about the as yet uncertain pathogenesis of s-IBM and h-IBM include the following two general possibilities. The first is that one "master gene" is activated, which in tum directly or indirectly activates the genes for all the accumulated proteins. The master gene could also diminish genetic expression of an enzyme or other factor important in protein disposal to enhance further the accumulation of the characteristic proteins. The master gene could be switched on (or a gene inhibiting it could be switched ofO in s-IBM by an environmental factor, such as a virus, and in h-IBM by the inherited abnormality.

The second possibility is that one protein is accumulated first because of excessive synthesis (excessive synthesis, *ie,* excessive mRNA, is known for PAPP [43••] and prion [Sarkozi *et al.,* Unpublished data)), decreased disposal, or both. Accumulation of this first protein leads, in some manner, to accumulation of the others, perhaps by the first protein's 1) acting as a transcription-activating factor for them via a common enhancer or promoter region on their genes, 2) binding to them **(eg,** apolipoprotein E and t are known to bind to AP *tn vitro* [47,481) or 3) impairing their catabolism.

The postsynaptic neuromuscular junction of a normal **innervated** mature muscle fiber is a morphologically and chemically specialized region induced, directly or indirectly, by the influence of the innervating motor neuron axon tips. At the human neuromuscular junction, there is a persistent normal accumulation of proteins that are abnormally accumulated in s-IBM and h-IBM, *ie,* PAPP [49), prion [SO•], <X1-antichymotrypsin [51), apolipoprotein E [52), fibroblast growth factor (37), transforming growth factor-P [42), ubiquitin (531, and the well-known nicotinic acetylcholine receptor and its 43-kD protein. Accumulation of PAPP mRNA is also increased at the neuromuscular junction [43.. l. Nonjunctional regions of mature human innervated fibers do not have accumulation of these proteins. At the normal neuromuscular junction some, or possibly all, of the characteristic "junctional proteins" are presumably continually synthesized under the influence of their activated genes in the special "junctional nuclei" of the muscle fiber. We propose that the orchestrated synthesis of the junctional proteins could be due to the persistent exuberant action (within the junctional muscle nuclei) of either a) a putative master gene conducting "junctionalization," and/orb) a "junctionalizing enhancer/promoter region" common to genes of the accumulated junctional proteins. In s-lBM and h-IBM, the accumulation of junctional proteins in nonjunctional regions of vaculoated muscle fibers could be caused by a similar exuberance of that master gene (or enhancer/promoter region) being provoked in nonjunctional nuclei, *ie,* a junctionalization of them by an environmental *(eg,* viral) or hereditary factor mimicking the action of the still unidentified neurogenic junctionalizing influence at the neuromuscular junction.

In regenerating human muscle fibers, a similar increase in the levels of some of the IBM proteins occurs, but to a lesser degree and in a more homogeneous pattern. This increase may be provoked by a partially similar gene activation mechanism. For example, in nonjunctional regions of human regenerating muscle fibers *in vivo,* PAPP immunoreactivity is expressed moderately, in a diffuse pattern (54) (unlike the strong multifocal pattern in IBM vacuolated muscle fibers). The accumulation of PAPP mRNA is also increased in these regenerating fibers [54,551, and PAPP mRNA is present in human myotubes in tissue culture, where it becomes downregulated during their development [551.

Neuropathy in sporadic inclusion-body myositis and hereditary inclusion-body myopathy

Transverse sections of every s-IBM and h-IBM biopsy specimen contain small angular muscle fibers that have dark staining with panesterase and NADH-tetrazolium reductase reactions and are considered to be indicative of denervation (4•,56); on electromyography, some patients have a neurogenic pattern 157) (any denervation of muscle fibers can result from a neurogenic or myogenous process [58]). In h-lBM, the histochemical evidence of denervation sometimes vastly predominates over vacuolated fibers or other definitely myopathic features (Engel and Askanas, Unpublished data), such that we are tempted to call it "hereditary inclusion-body myopathy-neuropathy." In s-IBM, we propose that the neuropathic component may fail to respond to immunosuppression.

Possible relevance to the pathogenesis of Alzheimer's disease

Because the same proteins that accumulate within the s-IBM and h-IBM muscle fibers accumulate in the brain in sporadic and hereditary Alzheimers's disease, the muscle diseases might have pathogenic analogies to Alzheimer's disease, and knowledge of one might help to elucidate the other. Within each organ disease group, the sporadic and hereditary forms are morphochemical phenocopies of each other. Between the two muscle and brain disease groups, perhaps the sporadic diseases involve parallel pathogenic mechanisms (possibly provoked by a viral process, an autoimmune process, or both) and the two hereditary subgroups involve similar mechanisms eventuating in the accumulated proteins.

One protein, prion, is not accumulated in the brains of patients with Alzheimer's disease but it is in the brains of patients with sporadic and hereditary prion diseases [591. In the prion brain diseases, the level of prion mRNA is not increased; instead, a unique non-mRNA mechanism of prion accumulation has been proposed [591. The muscle fibers of the IBMs are different from those of the prion brain diseases because they do have increased mRNA accumulation, suggesting that their increased level of prion protein is related to exuberance of the normal mRNA mechanisms of prion accumulation, which occurs normally in muscle fibers at neuromuscular junctions and during regeneration (Askanas *et al.,* Unpublished data).

Polymyositis

Clinical and pathologic considerations

Polymyositis is usually a sporadic disease that affects women more commonly than men (1,2,3••). Occasionally, more than one case occurs within a family, and other autoimmune disorders are not unusual among relatives 13..). Polymyositis usually causes symmetric proximal muscle weakness, sometimes associated with muscle pain and tenderness. Rarely, polymyositis can be accentuated focally, *eg,* as forearm swelling and soreness.

Without treatment, the disease is progressive, often leading to severe disability. Respiratory failure can occur due to respiratory muscle weakness and sometimes pulmonary fibrosis. The serum creatine kinase level is elevated and reflects leakage from only skeletal muscle fibers or heart, and creatine kinase-MB elevation can reflect leakage from regenerating skeletal muscle fibers or heart. (Elevations in the levels of the serum enzymes aspartate aminotransferase (SGOU, alanine aminotransferase (SGPU, and lactate dehydrogenase (LDH) are not organ specific-they can reflect leakage from skeletal muscle, heart, or liver cells. Therefore, to monitor the status of the liver, we routinely also measure levels of serum y-glutamyl transpeptidase (GGTP) because it reflects leakage from the liver but not muscle.) In polymyositis, electromyography shows a pattern of brief duration, small-amplitude, overly abundant motor unit action potentials that are often polyphasic [60), with some fibrillations. Diagnostic histochemical features of the muscle biopsy specimen include various degrees of muscle fiber necrosis and regeneration; perivascular and endomysial mononuclear cell infiltration; and increased amounts of endomysial and perimysial connective tissue, which typically is very positive with alkaline phosphatase [58). (Normally connective tissue is alkaline phosphatase negative, as it can be very early in polymyositis.) This alkaline phosphatase positivity probably reflects activated or proliferating fibroblasts. It is greater than in other myopathies with proliferated connective tissue, such as Duchenne's muscular dystrophy, which usually contains no or very little alkaline phosphatase positivity. We suspect that the amount of connective tissue alkaline phosphatase positivity in polymyositis and in dermatomyositis reflects the more rapid pace of fibroblast proliferation. Immunosuppressive treatment can rapidly reduce or eliminate inflammatory cells in polymyositis muscle biopsy specimens, but not their alkaline phosphatase positivity. Alkaline phosphatase positivity is also a feature of some activated/regenerative muscle fibers [61); however, it is not diagnostic because it is seen in regenerative fibers of any neuromuscular disease [61). Thus, regenerative/proliferative properties of both muscle fibers and fibroblasts are associated with alkaline phosphatase positivity.

Muscle biopsy immunopathology

The mononuclear cell infiltrates in polymyositis muscle biopsy specimens consist of T cells, macrophages, and to a lesser degree, B cells. The endomysial infiltrates are enriched in CDS+ T cells, whereas B cells are virtually absent; B cells are more common in the perivascular infiltrates (3..). Macrophages are present in all cellular infiltrations [2,3••) and can be identified by spe-

cific antibody or their high activity with the panesterase (nonspecific esterase) reaction.

Recently, a!P T-cell receptors were studied with in situ polymerase chain reaction in muscle biopsy specimens of 15 patients with polymyositis 162..]. Although a wide spectrum of T-cell receptor V gene rearrangements was present on the infiltrating T cells in both polymyositis and Duchenne's muscular dystrophy patients, the frequency of various V gene components was different in these two groups 162..). In a patient with a unique form of polymyositis, y/6 T-cell receptors were identified 163). The significance of these findings remains uncertain.

The location and type of the antigenic target of autoimmune attack in polymyositis are not known. Viruses are suspected to trigger the immune response, but this mechanism has not yet been convincingly documented. Enteroviral RNA was reported within the muscle fibers of patients with polymyositis 164], but other studies that used a sensitive polymerase chain reaction technique had negative findings 165,66]. Increased expression of HIA-DP antigen was shown in circulating T cells from polymyositis patients 167], and similar results were also found in various rheumatic diseases 168]. In polymyositis, muscle fibers express the major histocompatibility complex class I antigen, whereas normal fibers do not 1691. Muscle fibers in the vicinity of inflammatory foci can express major histocompatibility complex class II DR antigen (which is also not on normal fibers) 1701. Some of the polymyositis muscle fibers express intercellular adhesion molecule 1 170]. The pathogenic role of these antigens in polymyositis has not yet been defined.

Autoantibodies

Various circulating autoantibodies were reported in polymyositis 13••], but none are disease specific. Approximately 25% of polymyositis patients have antibody directed against a cytoplasmic histidyl transfer RNA synthetase 13••,71], also called anti-Jo-1 antibody. It is present in about 18% of polymyositis patients 171), and those with it have a high frequency of interstitial lung disease, arthritis, and Raynaud's phenomenon 171).

Antibodies against a signal recognition particle also occur in a few polymyositis patients who have a disease that is very severe and responds poorly to treatment 1721. No evidence indicates a direct pathogenic role of the circulating antibodies in polymyositis 171]; they may represent epiphenomena [1).

Summary

In summary, idiopathic polymyositis is an immune-mediated disorder of unknown cause. The factors that induce inflammatory response in the muscle tissue need to be identified. It is not known whether an altered muscle fiber itself instigates the inflammatory response or whether the muscle fiber is the unintended "bystander" victim of the immune attack. A role of intramu·scular ischemia in muscle damage is also possible. Although some patients still die of polymyositis, especially when it is associated with pulmonary fibrosis, polymyositis is often highly treatable. Various therapeutic approaches were recently extensively reviewed [3••]. One treatment we continue to find useful in patients in whom treatment with prednisone alone has failed is the addition of carefully adjusted and monitored oral cyclophosphamide (2 mg/kg/d) 173). The rapidly expanding knowledge of the interactions of cells and cytokines in the immune response should lead to more precise and effective treatments.

Dermatomyositis

Clinical and pathologic considerations

Adult dermatomyositis is more prevalent in women. A reddish or purplish skin rash often precedes muscle weakness. Dermatomyositis is sometimes associated with systemic sclerosis, mixed connective tissue disease, other systemic autoimmune diseases, and occasionally malignancies 11,3-J. Conversely, all 12 biopsied patients with lupus erythematosus had inflammatory myopathy histochemically typical of dermatomyositis 1741.

Muscle biopsy immunopathology

Mononuclear cell inflammation is often present in the dermatomyositis muscle biopsy specimen. Its degree varies among patients, and some very weak, untreated patients have virtually no inflammation 13.. ,741. Relatively few muscle fibers are surrounded or invaded by lymphocytes, which are mainly in the interstitial and perivascular areas. Unlike in polymyositis, the infiltrates contains a high proportion of B cells and CD4+ T cells 13.. J. Histochemically delineated perifascicular muscle fiber atrophy, involving both type I and type II muscle fibers, is a characteristic morphologic feature of dermatomyositis but is also seen in scleroderma 174) and lupus erythematosus 174). Alkaline phosphatase positivity of the connective tissue can also be prominent in dermatomyositis muscle.

The treatment of dermatomyositis has been summarized elsewhere (1,3.. ,73). Recently, intravenous immunoglobulin has been reported to be beneficial 175•], but one would like to find a less expensive long-term treatment. Intravenous immunoglobulin treatment does, however, raise interesting points about the possible mechanisms of benefit 175•].

Because angiopathy is well established in dermatomyositis muscle, dermatomyositis has been considered a primary vascular disease. The accumulation of complement, mainly C3, in muscle capillaries may be the earliest abnormality in dermatomyositis; it is usually followed by the involvement of the larger blood vessels (1,3.. ,76,771. Immune-mediated intramuscular an-

giopathy is considered to be responsible for capillary thickening, stenosis, and loss, causing ischemia that results in muscle fiber necrosis and perifascicular atrophy. Deposits of IgG and IgM in muscle blood vessels are common [1,3.. ,76,77], but the factors leading to complement activation and to complement and immunoglobulin deposition are not known. Although a humoral immune response directed against intramuscular blood vessels appears to play the important role in the pathogenesis of dermatomyositis, it is not yet known why the blood vessels of the muscles and skin are selectively targeted. Are these blood vessels "innocent bystander" victims of a humeral antibody attack intended for something else, such as a virus or bacterium not in vessels *(eg,* due to a shared antigen)? Or have some muscle or skin blood vessels been made "foreign" by an exogenous influence, making the ensuing humeral attack on them "normal"? When the first pathogenic steps are learned, more rational treatment might be devised.

Conclusions

Even though s-lBM, polymyositis, and dermatomyositis have various degrees of mononuclear cell inflammation in muscle biopsy specimens, the pathogenesis of each may be different. All three seem to have a dysimmune pathogenesis, possibly are of viral etiology, and probably involve genetic susceptibility factors of the patients. As more insight is gained into the molecular biology of each pathogenesis and etiology, better treatments should be able to be devised.

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