Chapter 5
Inclusion Body Myositis

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Abstract Inclusion body myositis is an insidious, slowly progressive myopathy of middle-aged and older individuals. Because of these characteristics, diagnosis is often delayed. Affected muscle is marked by the presence of rimmed vacuoles, inclusions, and an inflammatory infiltrate largely made up of CD8 T lymphocytes and macrophages. The inclusions contain beta-amyloid and phosphorylated tau protein, as well as other components. Theories of the pathogenesis of this disorder of older individuals include those based on evidence of the unfolded protein response leading to endoplasmic reticulum stress, abnormalities of proteosomal degradative function, mitochondrial dysfunction, the immune response, and amyloid toxicity. There is no proven, reliably effective medication for this disorder.

Keywords Inclusion body myositis • Beta amyloid • Tau protein • Endoplasmic reticulum stress • Unfolded protein response • MHC-1 • CD8 T cells

Introduction

The precise diagnosis of inclusion body myositis rests on biopsy findings, which have been recognized, over the last four decades, to be directly related to a distinct clinical syndrome. In 1965, Adams and coworkers ***(1)*** described the occurrence of nuclear and cytoplasmic inclusions in the muscle of a 20-year-old male student with a syndrome of progressive weakness of the extremities and trunk. Finger flexor strength was spared. Serum creatine kinase activity was mildly elevated. Biopsy of muscle demonstrated the presence of histiocytes and lymphocytes distributed perivascularly, interstitially, and around necrotic fibers. Of particular

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interest in this report was the presence of eosinophilic inclusions in the cytoplasm of myofibers and in sarcolemmal nuclei.

Two years later, Chou ***(2)*** reported findings of intracytoplasmic and intranuclear inclusions in myofibers of a 60-year-old man with chronic polymyositis, manifested by generalized progressive weakness, dysphagia, and muscle atrophy. Electromyograms suggested myositis, although serum enzyme levels were not significantly elevated. A mononuclear cell infiltrate was found in muscle on biopsy.

In 1970, a third case was reported by Carpenter and colleagues ***(3)*** of a 39-year-old woman, who had suffered from a progressive myopathy for 10 years. The onset of her weakness, which affected both proximal and distal muscles, was insidious. Her forearm and hand muscles, however, were strong. Serum creatine kinase values were normal. Cytoplasmic and nuclear filamentous inclusions were found in muscle on biopsy. In addition, this report called attention to the presence of vacuoles within the cytoplasm of myofibers.

In 1971, Yunis and Samaha ***(4)***, describing biopsy findings in muscle of a 26-year-old woman, suggested the name *inclusion body myositis*. This patient had weakness of both upper and lower extremities that developed over the course of several years. Although there was severe wasting in multiple areas, the strength of the quadriceps in the lower extremities and of the muscles of the hands was preserved. Serum creatine kinase levels were normal. Biopsy of muscle revealed the "typical picture of chronic polymyositis." Again, nuclear and cytoplasmic inclusions were found with a "focal and mild diffuse round cell infiltration." In their discussion, these investigators cast doubt on the previously suggested viral etiology of the filamentous nuclear and cytoplasmic inclusions. These reports, in the latter half of the twentieth century, laid the basis for the recognition of inclusion body myositis as a distinct clinical entity.

The present description of the typical patient recognized with this disorder, however, would be somewhat different from that of two of the patients initially reported. Inclusion body myositis is now understood to affect older individuals, with an insidious progressive myopathy that does affect the quadriceps and finger flexors as well as other musculature (see clinical finding discussion). Another early major advance in the delineation of this syndrome was the finding of Mendell and colleagues ***(5)*** of the presence of amyloid in the filamentous inclusions.

Clinical Findings

Inclusion body myositis is seen predominantly in middle-aged and older individuals, generally over age 50. However, it can occasionally occur in younger patients. It affects both sexes, although some series have noted a male preponderance. The disorder is marked by the insidious progression of painless weakness. Its slow progression may delay diagnosis and even its recognition by an affected individual. Many patients are seen late in the course of illness and are unaware that weakness is the result of disease rather than the natural consequence of aging. It is the occurrence of a fall, a misstep over a street curb, or the inability to negotiate a flight of stairs, which may bring the patient to seek medical attention. In many cases, it is a friend

or relative who points out the progressive weakness that an affected individual has experienced and suggests medical examination.

The delay in diagnosis was demonstrated in a report of patients with inflammatory muscle disease. There were 15 patients with inclusion body myositis; in these individuals, there was an average time of 6.5 years from the onset of disease to diagnosis ***(6)***. This was considerably longer than the delay noted for patients with dermatomyositis, which was 0.07 years on average. In this review, asymmetrical muscle weakness, with prominent wrist flexor, finger flexor, and knee extensor involvement were distinctive in comparison with the findings in those with dermatomyositis or polymyositis (Table 5.1).

Often on first meeting a patient with inclusion body myositis, the physician can note an unusually weak handshake, with the lack of firm finger grip, due to weakness of the flexors of the digits. Weakness of ankle dorsiflexors may have led to difficulty in walking, causing tripping or falling. This distal muscle involvement of both the upper and lower extremities is often a clue to diagnosis (Table 5.2).

In addition, however, many other muscle groups of the extremities and trunk and neck flexors also demonstrate weakness. Dysphagia is common late in the disease. Rarely, it may even be a presenting symptom ***(7, 8)***. Laboratory evaluation demonstrates elevation of the levels of the serum enzymes creatine kinase (CK), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) and of the serum myoglobin, but as indicated, these values may be unexpectedly low or even in the normal range. Electromyography indicates myopathic involvement. At this point, support for the diagnosis then rests on the muscle biopsy (Table 5.3).

Muscle Biopsy

Muscle biopsy findings are characteristic and diagnostic ***(9)***. Inclusion body myositis is a vacuolar myopathy, with cytoplasmic vacuoles rimmed by basophilic granules. In addition, an inflammatory infiltrate composed largely of CD8 T lymphocytes

Table 5.1 Clinical features

1. Age: Usually 50 or greater
2. Gender: Both sexes affected
3. Duration of illness: Over 6 months at presentation, often much longer

Table 5.2 Physical findings: Muscle weakness

1. Distal: Finger and wrist flexors, ankle dorsiflexors
2. Proximal: Trunk and shoulder musculature, hip and leg flexors
3. Weakness: May be asymmetrical

Table 5.3 Laboratory findings

1. Serum enzymes: CK, LDH, AST, ALT may all be elevated, CK most prominently, up to ten times normal, but may be lower and even within normal limits
2. Serum myoglobin: Moderately elevated

Table 5.4 Muscle biopsy findings

1. Rimmed cytoplasmic vacuoles
2. Cytoplasmic and nuclear inclusions
3. Presence of amyloid
4. Ragged red fibers
5. Variable fiber size, angulated fibers
6. Necrotic and regenerating fibers
7. Inflammatory infiltrate of lymphocytes and macrophages
8. Cytoplasmic and nuclear filamentous inclusions seen with electron microscopy (electron microscopy usually not necessary for diagnosis)

and macrophages is present. Filamentous inclusions in both the cytoplasm and nuclei of myofibers are seen on electron microscopy. These inclusions, which are eosinophilic, on light microscopy contain beta-amyloid and phosphorylated tau protein. There is a mitochondrial disorder marked by the presence of ragged red fibers and also manifested by increased numbers of myofibers that lack cytochrome oxidase. In this regard, electron microscopy reveals abnormal mitochondria, and genetic techniques have demonstrated an increase in the number of mitochondrial DNA deletions in affected patients. Muscle fiber size is variable; there are groups of angulated fibers and necrotic as well as occasional regenerating fibers. The findings of typical changes by light microscopy usually suffice for diagnosis, and electron microscopy, although providing powerful insight into disease morphology, is generally reserved for research and not employed in general practice. These findings, although characteristic, may be variably present in individual biopsy samples, and can, in certain samples, be difficult to discern (Table 5.4).

Pathogenesis

Theories of pathogenesis take into account two major pathological features present in affected muscle: the degenerative component (the vacuoles and inclusions) and the inflammatory component (the lymphocytic and macrophagic infiltrate). These theories may be thought of as concentrating on toxic-metabolic factors and on the immune response.

Toxic-Metabolic Factors

Askanas and Engel ***(10)*** pointed out that myofiber degeneration in this disorder is characterized by progressive fiber atrophy and vacuolization, with accumulation of multicomponent aggregates, the amyloid-containing inclusion bodies.

The amyloid inclusions are of two types, one of which contains amyloid beta and the other phosphorylated tau protein. In addition, both types of inclusions

contain other proteins. These other proteins are thought to be subject to misfolding in the endoplasmic reticulum, leading to abnormalities in function of this intracellular organelle, a mechanism that can result in stress within the cell. This stress-producing process has been termed the *unfolded protein response*. Further evidence for the possible role of endoplasmic reticulum stress within affected myofibers is suggested by the presence of chaperone proteins in the inclusions. These proteins would otherwise assist in the folding of newly formed polypeptides. Their presence in inclusions has been taken to be an indication of the unfolded protein response and of endoplasmic reticulum stress. This stress-evoking process may set in motion a series of pathogenic events, including the induction of mystatin, a factor in muscle atrophy, and the expression of major histocompatibility complex (MHC) by myofibers. This last factor in turn may play a role in the elicitation of the immune response.

The presence of proteasomal components, and of ubiquitin and mutated ubiquitin in inclusions, indicates abnormalities in the cell's catabolic processes. Also present are alpha synuclein and presenilin 1, markers of oxidative stress, and heat shock proteins. These constituents of the inclusions are indicative of several coexisting abnormalities in the metabolism of affected muscle cells. The vacuoles represent autophagosomes filled with membranous debris, a sign of incomplete cellular processing or catabolism.

Askanas and Engel ***(10)*** emphasized the importance of amyloid beta precursor protein and of its metabolyte, the proteolytic fragment amyloid beta, as toxic upstream factors in the cascade of degenerative processes, which results in the findings mentioned that are characteristic of inclusion body myositis.

Amyloid beta, in experimental studies, has been shown to act as a toxin on myofibers, leading to vacuolization, atrophy, and changes typical of those seen in inclusion body myositis. Moreover, there is evidence of increased transcription of amyloid beta precursor protein in muscle of patients with inclusion body myositis. Beta amyloid may accumulate as the result of abnormalities found in components that otherwise could process it. These include the secretase enzymes (which cleave amyloid beta), free cholesterol (which may influence amyloid beta deposition), cystatin C (a protease inhibitor), and transglutaminases 1a and 2 (which may allow cross-linking of amyloid beta molecules). All of the foregoing factors are thought to account for the accumulation of amyloid beta, a toxic material, in myofibers.

There is also evidence of oxidative stress and free-radical toxicity and of inhibition of normal proteasome function. The last abnormality is indicated by the presence of both ubiquitin and mutated ubiquitin in the inclusions. Inhibition of proteasomal function has also been suggested to be related to amyloid beta. Also, as indicated, significant mitochondrial abnormalities are present in affected muscle.

How these processes are linked, and the order of their appearance in the pathogenesis of inclusion body myositis, awaits further research. At present, the manifestations of this disorder are felt to be due to cascades of multifactorial, toxic, pathological events.

The Immune Response

As reviewed by Dalakas ***(11)***, in addition to the vacuoles and inclusions, muscle tissue in inclusion body myositis contains an inflammatory infiltrate made up in large part of macrophages and cytotoxic CD8 T lymphocytes, which can be seen invading intact myofibers. Other features of inclusion body myositis suggest its association with autoimmune disease.

In approximately 20–30% of patients, another disorder considered to be autoimmune may be present. Autoimmune disorders that have been observed include autoimmune thyroid disease, multiple sclerosis, rheumatoid arthritis, and Sjögren's syndrome. An increased frequency of genes associated with autoimmunity, such as human leukocyte antigen (HLA) DR3, has been found in up to 75% of patients. Moreover, a genetic factor in disease susceptibility is suggested by the rarely observed occurrence of inclusion body myositis in twins and in other family members of affected individuals ***(12)***.

In his review, Dalakas ***(11)*** pointed out that there have been cases of inclusion body myositis associated with dysproteinemia, paraproteinemia, and immunodeficiency syndromes, again suggestive of a relation of disease susceptibility to altered immune mechanisms. Also, there have been reports of inclusion body myositis in patients infected with HIV and human T-lymphotrophic virus 1 (HTLV-1), both agents which may alter normal immune mechanisms.

Overexpression of MHC antigens occurs in muscle of patients with inclusion body myositis. Under normal circumstances, myofibers do not express detectable amounts of MHC. Along with the upregulation of MHC, T-cell activation is present, with expression of ICAM-1 (intercellular adhesion molecule-1), MHC-1, and ICOS (inducible costimulatory molecule). The activated, cytotoxic T cells, which invade myofibers, display perforin granules capable of inducing fiber necrosis. Moreover, there is evidence (based on T-cell receptor types) that the cytotoxic T-cell population has been specifically recruited to muscle and locally expanded there after exposure to antigen.

Taken together, these findings suggest that muscle fibers can act as antigen-presenting cells to CD8 lymphocytes. There is also evidence of upregulation of chemokines, cytokines, and metalloproteinase in muscle, all of which may contribute to myofiber damage. The presence of activated, cytotoxic, antigen-driven, T-cell populations in muscle of genetically susceptible individuals points to the likely importance of immune mechanisms in the disorder (Table 5.5).

Table 5.5 Pathogenetic factors

Toxic-metabolic factors	Immune-inflammatory factors
Amyloid beta	Invasion by activated, cytotoxic lymphocytes
Mitochondrial disorder	MHC expression on myofibers
Oxidative stress	Upregulation of cytokines, chemokines, and metalloproteinases
Proteasomal abnormality	
Endoplasmic reticulum stress	

Summary of Theories of Pathogenesis

Based on our present knowledge, in inclusion body myositis, it is likely that the two processes, those involving toxic-metabolic factors (related, at least in part, to amyloid beta) and immune-inflammatory mechanisms (related to cytotoxic T lymphocytes), may be acting concurrently. The stimulus or factor responsible for the initiation of these processes remains unknown, however. Whether one of these two processes is secondary to the other or whether they act synergistically in production of disease still remains to be determined. Further, intriguing hypotheses of a putative role of aging, genetics, or a possible, as yet unknown, infectious agent, remain open for investigation.

Therapy

Presently, there is no therapy that has been reliably effective. A number of agents, including corticosteroids, cytotoxic-immunosuppressive agents, anti-TNF (tumor necrosis factor) agents, interferon beta, and intravenous gamma globulin, have been tried. In some cases, there have been modest gains, but overall there has been no dependably effective therapeutic approach to this disorder. However, it is possible that some patients who demonstrate marked signs of inflammation (such as markedly elevated enzymes or serum myoglobin and an exuberant infiltrate on biopsy) or those with rapidly progressive disease may obtain benefit from treatment. Many physicians, on initial diagnosis, will employ a course of therapy with careful ongoing assessment to determine whether there may be some benefit to be attained in individual cases.

The lack of success of measures designed to address autoimmunity has been suggested by some to indicate that immune mechanisms may not be central to disease initiation or perpetuation. This is an area requiring further investigation.

It is likely, however, that the presence of irreversible degenerative mechanisms, perhaps related at least in part to aging, as well as the late stage of illness at which many patients are first seen may be important factors in the poor response to therapy so characteristic of this disorder. This underscores the need for knowledge of the modifiable, pathological pathways in inclusion body myositis.

Beyond consideration of therapeutic measures aimed at pathogenetic mechanisms in this disorder, in the elderly patient attention should be paid to nutrition, physical therapy, and remediation of any existing comorbidities.

Hereditary Inclusion Body Myopathy

Although inclusion body myositis may at times be familial, it should not be confused with hereditary inclusion body myopathy. This last name is applied to a number of different genetic disorders, which may be autosomal, recessive, or dominant and

can appear in childhood or later in life. The biopsy findings, although similar, do not include an inflammatory infiltrate, and there is no upregulation of MHC markers in muscle tissue.

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