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Inclusion Body Myositis: Evolving Concepts

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Abstract

Purpose of review—To discuss recent developments in our understanding of epidemiology, diagnostics, biomarkers, pathology, pathogenesis, outcome measures and therapeutics in Inclusion Body Myositis.

Recent findings—Recent epidemiology data confirms a relatively higher prevalence in the population aged above 50 years and the reduced life expectancy. Association with cancer and other systemic disorders is better defined. The role of magnetic resonance imaging and ultrasound in diagnosis as well as in following disease progression has been elucidated. There are new blood and imaging biomarkers that show tremendous promise for diagnosis and as outcome measures in therapeutic trials. Improved understanding of the pathogenesis of the disease will lead to better therapeutic interventions, but also highlights the importance to have sensitive and responsive outcome measures that accurately quantitate change.

Summary—There are exciting new developments in our understanding of inclusion body myositis which should lead to improved management and therapeutic options.

Keywords

Inclusion Body Myositis; pathophysiology; pathology; diagnostics; antibodies; therapeutics; spectrum disorder; polymyositis; HIV

Introduction

While controversy remains on whether inclusion body myositis (IBM) is primarily an immune or a myodegenerative disorder, recent papers have defined strong autoimmune and inflammatory underpinnings, suggesting the inflammatory component may be the herald of disease. Herein we review the evolving understanding of IBM pathophysiology, in particular the role of immunosenescent lymphocytes, and the current understanding of IBM epidemiology, new diagnostics, biomarkers, and therapeutic trials.

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Epidemiology

The prevalence of IBM is 18.20 per 100,000 people above the age of 50 years. IBM is associated with a lower life expectancy, compared to aged match population.(1–3) Disability is due to severe bulbar dysfunction (requiring feeding gastrostomy in over 50%) and motor dysfunction resulting in wheelchair confinement in >50% within 10 years of symptom onset. One third of patients have peripheral neuropathy (2.7 times more likely than matched population) and 6% have Sjogren's syndrome (6.2 times more likely than matched population). There is no increase in incidence of solid tumors, IBM patients are 3.9 times more likely to have a hematologic malignancy than population controls, and there is an association with T-cell large granular lymphocytic leukemia.(2) Respiratory failure, often related to pneumonia, is the most common cause of mortality.(1) Patients with IBM remain a very motivated group. The majority are willing to undergo multiple visits and study-related procedures without compensation, including muscle biopsy solely for research use.(4)

Diagnostics

One third of IBM patients demonstrate abnormalities on conventional electrodiagnostic studies and half show abnormalities on thermal thresholds. Median nerve motor and sensory excitability are significantly different in IBM patients compared to normal controls.(5) Clinical markers of motor severity and myotonic discharges on EMG correlate with the degree of inflammation on muscle biopsy.(6) Motor unit potential (MUP) duration inversely correlates with all clinical measures.(6) On Computerized Tomography (CT) studies, the differential involvement of the anterior compared to the posterior thigh muscles correlates well with a clinical diagnosis of IBM.(7) Similarly, muscle edema on muscle magnetic resonance imaging (MRI) highly correlates with increased amounts of muscle inflammation on muscle biopsy.(8)

Important work from the London group showed that inflammation in IBM muscle may be responsible for subsequent fatty infiltration and MRI parameters are most response sensitive to change with time. Using serial quantitative MRI (qMRI) one year apart in 26 individuals with IBM and correlating MRI data with measures of muscle function, they confirmed a reduction in muscle volume and muscle T2 in a one year, with a concomitant increase in all measures of fatty infiltrates. The increase in fat signal inversely correlated with decrease in muscle T2. The worsening of the muscle MRI parameters inversely correlated with decline in muscle function measures.(9) Muscle ultrasound also shows significant accuracy in terms of detecting fatty infiltration and appears to be a good tool to differentiate IBM from other idiopathic inflammatory myopathies.(10, 11)

Biomarkers

Autoantibodies to NT5c1A is a sensitive and highly specific serological marker for IBM. (12, 13) Recent studies show association with a more severe motor phenotype, dysphagia, reduced survival and more cytochrome oxidase negative myofibers and auto-aggressive inflammation on muscle biopsy. (14) However, other studies have not find the same associations and showed that NT5c1A antibodies can also be seen in dermatomyositis,

antisynthetase syndrome and immune mediated necrotizing myopathy. There is no association between anti-NT5c1A autoantibodies and malignancy or interstitial lung disease.(14–17) An ongoing NIH-funded two-year observational study is examining the influence of this serological biomarker on the natural history of IBM (NCT05046821). IBM is more common in Sjogren's syndrome patients with myositis and these patients have much higher rates of NT5c1A seropositivity.(18)

There is a high prevalence of "immunosenescent" (i.e., chronically overstimulated and exhausted T cells that have lost capacity to undergo apoptosis) highly differentiated T cells in blood and skeletal muscles in IBM, and these T cells are proposed as a highly sensitive IBM biomarker.(19) These highly differentiated CD8+ KLRG1+ T cells show the highest sensitivity for IBM and can be used as a diagnostic marker.(19–22) Correlative studies exploring KLRG1 influence on disease behavior (NCT05046821) are in process. Given the loss of capacity to undergo apoptosis, these T cells are not likely to respond to conventional immunosuppressants. An early phase therapeutic trial aimed at selectively depleting CD8+ KLRG1+ T cells in IBM is currently underway (NCT04659031).

Potential imaging biomarkers in IBM in addition to MRI(23) include electrical impedence myography (EIM). In a cross-sectional study, EIM measures of multiple muscles correlated with several muscle and disease related functions in IBM, discriminated IBM from healthy control muscles correlated well with clinical outcome measures.(24) Positron-emission tomography (PET) using either amyloid or tau based ligands have shown promise.(25–27) An exciting new technology provides targeted imaging of CD8+ T cells using a radiolabeled minibody against CD8+ T cells (89Zr-Df-IAB22M2C). It appears safe, well tolerated and shows more intense uptake in relevant muscles in IBM compared to the general population or cancer patients.(28)

Pathology

IBM is pathologically defined by the 2011 ENMC-IBM criteria, with the constellation of histologic features including endomysial lymphocytes with or without nonnecrotic myofiber invasion, rimmed vacuoles, and intracellular protein aggregates or tubulofilaments.(29) Other important histologic findings in IBM muscle biopsies include severe myopathic "dystrophy-like" changes,(30) mitochondrial pathology, MHC class I and II immunopositivity, and p62 positivity, particularly in discrete subsarcolemmal or perivacuolar aggregates.(31) While subsarcolemmal p62 accumulation is characteristically present in IBM muscles, it is not a specific marker for IBM, but rather p62 accumulation is a general response to muscle injury which becomes more prevalent with more severe damage (32). Hedberg-Oldfors et al recently provided important characterization of IBM mitochondrial pathology using deep sequencing and quantitation of mtDNA variants, which revealed markedly increased levels of large deletions and duplications in IBM muscles, as well as increased somatic single nucleotide variants and reduced mtDNA copy numbers. The distribution and type of variants were similar in IBM muscle and controls, suggesting an accelerated aging process in IBM.(33)

IBM histopathology is also shared with associated diseases, such as HIV, Hepatitis C, Sjogren's and granulomatous myositis. For example, the co-occurrent finding of granulomatous myositis plus characteristic histologic features of IBM has long been reported in patients with or without sarcoidosis and/or extramuscular involvement.(34) Clarifying these interactions could aid our understanding of IBM pathophysiology.

Pathogenesis

Advances in understanding pathological mechanisms of IBM have centered on elucidating the molecular features. Using RNA sequencing, Ikenaga et al., found that CDH1, which encodes the epidermal cell junction protein cadherin 1, was overexpressed in IBM muscles, but is rarely seen in muscles of other idiopathic inflammatory myopathies.(35) Amici et al studied gene expression changes across different myositis subtypes by creating a myositis transcriptome from patients with the major clinical and serological disease subtypes of idiopathic inflammatory myopathies, including IBM.(36) From this myositis transcriptome they generated a co-expression network of 8101 dynamically regulated transcripts into a map of gene expression modules of interrelated biological processes and disease signatures. They found that universally myositis-upregulated network modules included muscle regeneration, specific cytokine signatures, the acute phase response, and neutrophil degranulation, while myositis subtype-specific modules included type 1 interferon signaling and titin in dermatomyositis, RNA processing in antisynthetase syndrome, and vasculogenesis in IBM.(36)

Recent studies highlighting specific immunological perturbations in IBM, including the presence of plasma cells and clonally-restricted immunoglobulin transcripts in IBM muscle, and the discovery of autoantibodies, has rekindled the argument that inflammation may be the primary driver of the disease.(37) The development of IBM-specific pathology in myotube cultures and mouse muscles from passive transfer of serum from NT5c1A seropositive IBM patients further bolstered this concept.(38) Recent work showed development of greater fatty infiltration in areas of muscle with greatest STIR signal (reflective of inflammation) also lends support that inflammation drives the "degeneration".(9) Discovery of a potent and specific type I interferon and interferon gamma associated pathways in IBM, based on pathologic as well as transcriptomic and proteomic studies, point to a specific immune-interaction between immune cells (particularly macrophages) and myofibers in IBM.(36, 39–41). Recent work has shown a strong association with three Class II MHC (HLA-DRB1) alleles, with particularly strong association with HLA-DRB1*03:01, and the risk could be largely attributed to amino acids within the peptide binding pocket.(42) A similar strong association with HLA-DRB1 was seen in the Japanese population.(43) No association with NT5c1A antibodies was seen in either populations.(42, 43) History of previous Hepatitis C (HCV) infection is also pervasive in Japanese sIBM patients but not seen in North American patients.(1, 44)

Unfortunately, lack of a viable animal model is a significant limitation in IBM studies. An animal model of a related disorder, VCP myopathy, recapitulates some of the degenerative changes of IBM, but lacks the inflammatory component crucial to IBM. (45) Similar limitations have plagued prior IBM animal models.(46–49) A mouse xenograft model of

IBM by Lloyd et al., represents a major step forward in modeling of human disease. They created xenografts of human muscle by transplanting human muscle biopsies from IBM patients into nude mice.(50) Although not a perfect model, with some of the pathological features resembling graft-vs-host reaction, it represents a major advance in our ability to better understand the disease by allowing study of the inflammatory and degenerative changes in muscle ex vivo. The predominance of highly differentiated CD8+ T cells was confirmed in the model and the model is amenable to different interventions. Anti-CD3 monoclonal antibodies (OKT3) significantly eliminated muscle inflammation, but did not affect the degenerative pathology.(50) While it is possible the inflammatory changes set off an autonomous degenerative process that cannot be reversed after inflammation resolves, further work is needed to determine whether the inflammatory or degenerative changes are primary.

Transformation of clinical and immunological phenotype and whether IBM is truly a spectrum disorder is also an evolving concept. HIV-associated Polymyositis/IBM complex is an example of potential transformation, wherein the disease starts as a treatment-responsive proximal symmetric disorder associated with endomysial CD8+ T cell dependent inflammation with auto aggressive features and variable mitochondrial abnormalities, but without rimmed vacuoles and protein accumulation on muscle biopsy. (51). Ultimately, these patients develop an asymmetric disorder, with typical finger flexor and quadriceps involvement, rimmed vacuoles and protein accumulation on muscle biopsy (51, 52), and become treatment unresponsive. Similar evolution has now been reported in patients originally diagnosed with PM-Mito,(53) with an IBM-like phenotype with abundant mitochondrial changes but no rimmed vacuoles on muscle biopsy. There is progressive development of IBM pathology in these patients, including rimmed vacuoles and protein deposits, and an evolving clinical phenotype including development of dysphagia, suggesting that PM-Mito may be **early IBM** (Stenzel W – personal communication) which later evolves into full-blown IBM.(54) High frequency of antibodies to NT5c1A are common to both PM/IBM and PM-Mito.(15, 51) It is tempting to speculate that the evolution in HIV-related PM/IBM and in PM-Mito may be related to an evolution of the immunophenotype in these patients, where the clinical transformation parallels the immunophenotypic transformation to highly differentiated T cells in blood and muscle (Figure 1).

Outcomes Measures

There remains a paucity of data on the natural history of disease in IBM. Recent papers attempted to address this but suffered from inconsistent methodology, e.g., non-uniform protocol, different evaluation methods at different sites and a mish mash of data. Sangha et al. provided “natural history” data on the largest number of patients to date (181 subjects with a median of 7 years of follow up), but the paper represents data from three disparately different studies, at different sites, under different protocols and at different timelines.(55) Oldroyd et al. provided an estimate of long term projection of strength and functional status based on linear modeling and showed that age of onset clearly influenced decline of some motor functions (grip was worse in younger onset patients, while knee extension strength was worse in older onset patients).(56) A number of the traditional outcome measures

used in neuromuscular disorders are not sensitive enough to reliably detect changes in IBM and are not validated in this population (57) There are efforts ongoing to validate existing and new outcome measures in IBM, including 2-minute walk test, timed up and go, 4-stair climb, PROMIS, upper extremity and hand functions.(57) The optimal muscle strength testing method has also not been validated. Most studies focus on lower extremity functions or walking/ambulation as an outcome measure, but not enough attention is paid to upper extremity functions and related disability. Two important papers quantitated these disabilities for the first time, and showed that the current upper extremity questions in the IBM Functional Rating Score (IBMFRS) correlate poorly with finger flexor strength and grip strength.(58) A new Inclusion Body Myositis Patient-Reported Outcome measures for upper extremity function was devised, which performed much better in terms of upper extremity/hand functions and correlated more strongly with grip and pinch strength than the IBMFRS.(59)

Therapeutics

Unfortunately, therapeutic interventional trials have failed to show benefit in IBM. Bimagrumab, a fully humanized monoclonal antibody that antagonizes Activin II receptor (AcIIR), did show an increase in muscle volume at the end of the treatment period, but this increase did not result in muscle strength or functional improvement and failed its primary outcome measure of improvement in 6 minute walk distance (6MWD) at 52 weeks.(60) A longer extension study found the drug to be safe and tolerable up to 2 years but did not show motor or functional improvement.(61) Arimoclomol, a heat shock protein inducer and protein stabilizer, showed preliminary evidence for benefit in a phase II study in IBM(45) and was carried into a phase III registration trial in IBM. This study recently concluded and showed no benefit in any parameters studied and had significant investigational drug-related adverse events that lead to early discontinuation in a number of subjects.

Use of blood-flow restricted resistance training (BFRT) as treatment is gaining popularity in IBM but objective data is lacking. A single randomized clinical trial in 22 patients in one center in Denmark showed that patients undergoing BFRT reported no change in self-reported or objective physical functions. Compared to control muscles, BFRT treated muscles showed no decline in muscle strength, suggesting stabilization, and there were no changes in thigh lean mass.(62) There were no findings to support satellite cell activation or an increase in myonuclei.(63) Similarly, there was no change in muscle fiber cross sectional area and intramuscular capillary density.(63) Functional studies to assess molecular pathways are lacking, but a single study showed attenuation of the myostatin pathway from short-term BFRT.(64) Given the paucity of data at this point, potential benefits from BFRT should be interpreted with caution.

Dysphagia remains a significant problem in IBM and contributes to the morbidity and mortality. Presence of a pharyngeal bar on video fluoroscopic studies appears to have high specificity for IBM (96% vs. a sensitivity of 33%).(65) Objective improvements in swallowing have been demonstrated following both endoscopic and transcervical cricopharyngeal myotomy in IBM.(66) In a study of EMG-guided chemodenervation of cricopharyngeal muscles with botulinum toxin A in patients with IBM and Oculopharyngeal

Muscular Dystrophy (OPMD), the majority of patients reported improvement on a dysphagia questionnaire.(67) Over half felt subjective improvement but there was no change on timed cold water swallow test.

Conclusion

There have been significant recent advances in our understanding of IBM pathophysiology and the role of immune cells in IBM pathogenesis. The role of immunosenescent T cells is better defined and trials aimed at immunologically depleting these cells are underway. The concept of IBM as an evolving spectrum may change our approach and diagnosis of early-stage disease and may lead to more aggressive treatment of early phenotypes. Data on the natural history of IBM is lacking, and more sensitive and specific IBM biomarkers and outcome measures are needed.

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Conflicts of Interest:

Dr. Mozaffar discloses an advisory role for and/or receiving research funds from Alexion, Amicus, Argenx, Arvinas, Audentes, AvroBio, Horizon Therapeutics, Immunovant, Maze Therapeutics, Momenta (now Janssen), Sanofi-Genzyme, Sarepta, Spark Therapeutics, UCB, and Modis/Zogenix. Dr. Mozaffar also serves on the data safety monitoring board for Acceleron, Avexis, and Sarepta

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Key Points

- Controversies remain as to whether IBM is primarily an inflammatory disorder vs. primarily a myodegenerative disorder
- Multiple new lines of evidence further cement the concept of inflammation driving the degenerative aspects of the disease
- The role of immunosenescent, exhausted, highly differentiated T cells is better defined; therapies are in development to target these T cells as well as strategies to upregulate regulatory T cells
- MRI aids the diagnosis the disease and may also be an excellent outcome measure for clinical trials
- The mouse xenograft model is a major step forward and will help carry out pre-clinical studies of the disease. Elimination of inflammation in this model does not necessarily stop the degenerative processes, suggesting that there may be a “point of no return”, where degeneration becomes self-sustaining

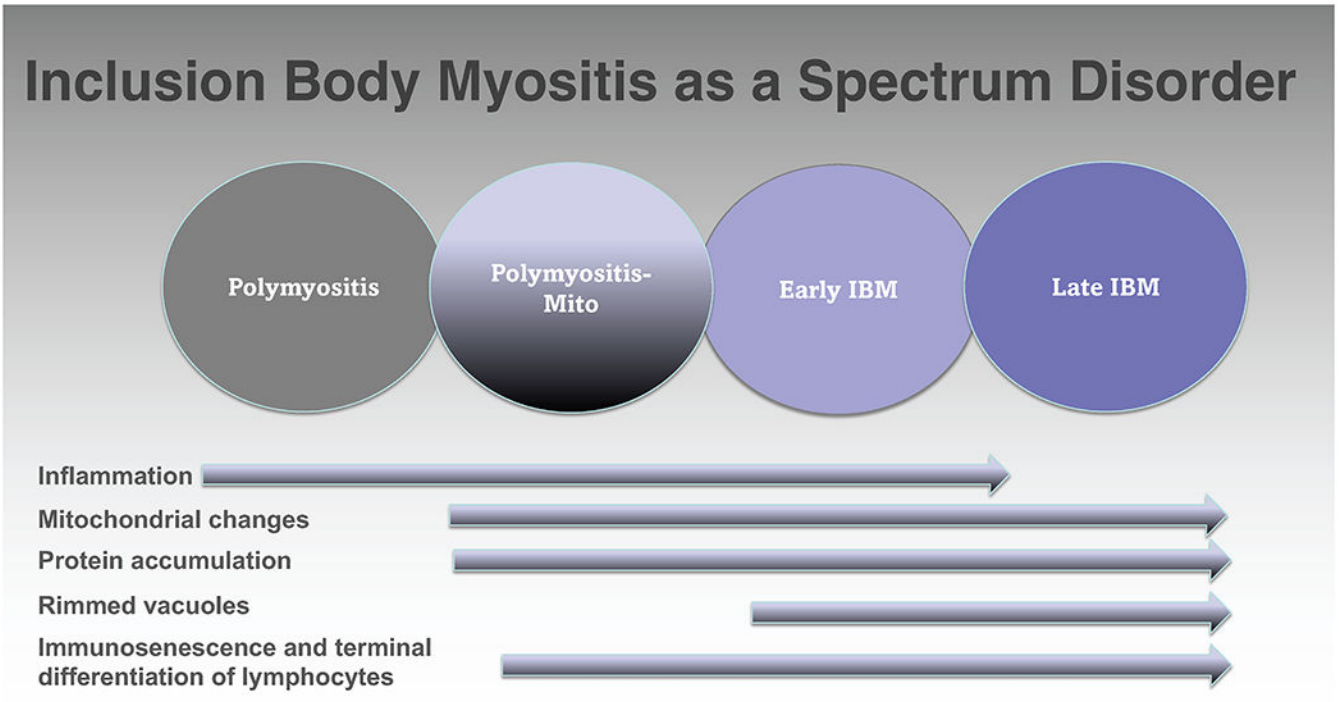

Figure 1:

A conceptual framework for disease overlap and spectrum in polymyositis/Inclusion Body Myositis. In some patients disease phenotype morphs, and is associated with a progressive increase in 1) percentage of immunosenescent highly differentiated (apoptosis-resistant) T lymphocytes, 2) mitochondrial deletions and myopathological features of mitochondrial dysfunction, 3) rimmed vacuoles, and 4) accumulation of a **vast array** of proteins, including p62, TDP-43, etc. Inflammatory infiltrates generally reduce over time as the above changes occur.