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Inclusion body myositis

IBM as an autoimmune disease

Evidence that IBM is an autoimmune disease includes the presence of predisposing immunogenetic risk factors, a large number of antibody-secreting plasma cells within IBM muscle tissue, and the frequent occurrence of auto-antibodies recognizing the NT5C1A protein in the blood of patients with IBM. Furthermore, the observation that cytotoxic CD8 + T cells surround and invade muscle fibres in IBM muscle specimens provided early evidence that muscle damage could be mediated by T cells. Indeed, subsequent studies revealed that CD8 + T cells are clonally expanded in muscle tissue and that the same clones are found in both blood and multiple muscles from the same patient, where they persist. Although the T cell targets remain unknown, these findings suggest that T cell stimulation by the relevant auto-antigen persists for years in these patients. Interestingly, some of the T cell clone identities are shared between different patients with IBM, suggesting a common as yet undefined target auto-antigen among those with IBM. Importantly, studies showed that both CD4+ and CD8 + T cells in patients with IBM have unusual properties, including aberrant loss of CD28 or CD5 expression with the gain of CD16, CD94 and CD57 expression that is associated with terminally differentiated T cells. Phenotypically similar to the abnormal lymphocytes seen in patients with T cell large granulocytic leukaemia, the infiltrating T cells in IBM would also be expected to have increased cytotoxic potential and resistance to apoptosis. These features may help explain why IBM is refractory to glucocorticoids and other immunomodulatory therapies but this population of T cells could also be a promising target for therapeutic intervention.

In addition to the invasion of myofibres by CD8+ CD57+ T cells, IBM muscle specimens are notable for the presence of rimmed vacuoles and protein inclusions within muscle fibres. For example, in one study, aggregates of p62 and TDP43 proteins were found in 12% of IBM myofibres but only rarely in those of other IIM subtypes. Although other reports suggest that p62 accumulation may be a non-specific feature of IIM, TDP43 positivity is

recognized as highly specific for IBM. Hence, IBM might have a considerable degenerative component but it has not been shown whether the accumulation of these proteins would lead to muscle cell degeneration. Furthermore, it remains unclear whether these changes occur in response to intensive immune-mediated damage or reflect some other underlying non-immune pathological process.

Diagnosis, screening and prevention Clinical subgroups

IBM is clinically characterized by asymmetrical weakness of both proximal and distal muscles that often includes the quadriceps and long finger flexors (Fig. 6). IBM occurs mainly in individuals >50 years of age. Dysphagia occurs in >50% of patients, whereas other extramuscular manifestations are rare. Hallmarks of muscle histopathological findings include endomysial T cell infiltrates and vacuoles rimmed by membranous cytoplasmic material. IBM can be associated with Sjögren syndrome and other connective tissue diseases. The co-occurrence of IBM with sarcoid myopathy has also been reported. IBM progresses slowly over decades and does not usually respond to immunosuppressive therapy.

Diagnosis

The European Neuromuscular Centre (ENMC) IBM research diagnostic criteria were proposed in 2011 and recognize clinicopathologically defined IBM as well as clinically defined IBM and probable IBM. Diagnosis is based on the variable presence of combined or separate knee extension weakness equal to or greater than hip flexion weakness and finger flexion weakness greater than shoulder abduction weakness, together with age and duration limits and histopathological features in muscle tissue. The newest IBM diagnostic criteria use evaluation of finger flexor or quadriceps weakness, endomysial inflammation, and either invasion of non-necrotic muscle fibres or presence of rimmed vacuoles.

Management

Unlike DM and PM, IBM is typically refractory to immunotherapy. Although glucocorticoids and other immunosuppressive therapies have not been tested in randomized controlled trials, the general consensus is that they are not efficacious, even though glucocorticoids may improve muscle enzyme levels in the short term and dysphagia in some patients. IVIg might slow disease

progression but its long-term effectiveness remains unclear. Methotrexate, which is commonly used in other forms of myositis, failed to slow the progression of muscle weakness in a small, randomized, double- blind, placebo- controlled study in patients with IBM. Intravenous bimagrumab, an anti- activin type II receptor antibody, was evaluated in the largest phase III clinical trial in IBM to date and failed to meet its primary endpoint of 6-minute walk distance at 52 weeks. Pilot studies of arimoclomol, which co-induces the heat shock response by prolonging the activation of heat shock factor 1 and may promote normalization of protein handling within muscle, and rapamycin (sirolimus), which inhibits protein kinase that regulates several intracellular processes, including survival, protein synthesis and autophagy, have shown encouraging results but these have not been confirmed. Unfortunately, a phase II/III clinical trial of arimoclomol in IBM failed to meet its primary endpoint; however, a phase III clinical trial of rapamycin is ongoing. Exercise is currently the only treatment, which has consistently shown a varied degree of benefit in IBM, although the optimal type of exercise programme is yet to be determined.

Quality of life

The IBM Functional Rating Scale (IBMFRS) was created and validated for patients with IBM. However, the indices were assembled from the provider viewpoint with little patient involvement in their construction or improvement and review of the survey instrument by myositis patients revealed that they deemed some questions vague or irrelevant.

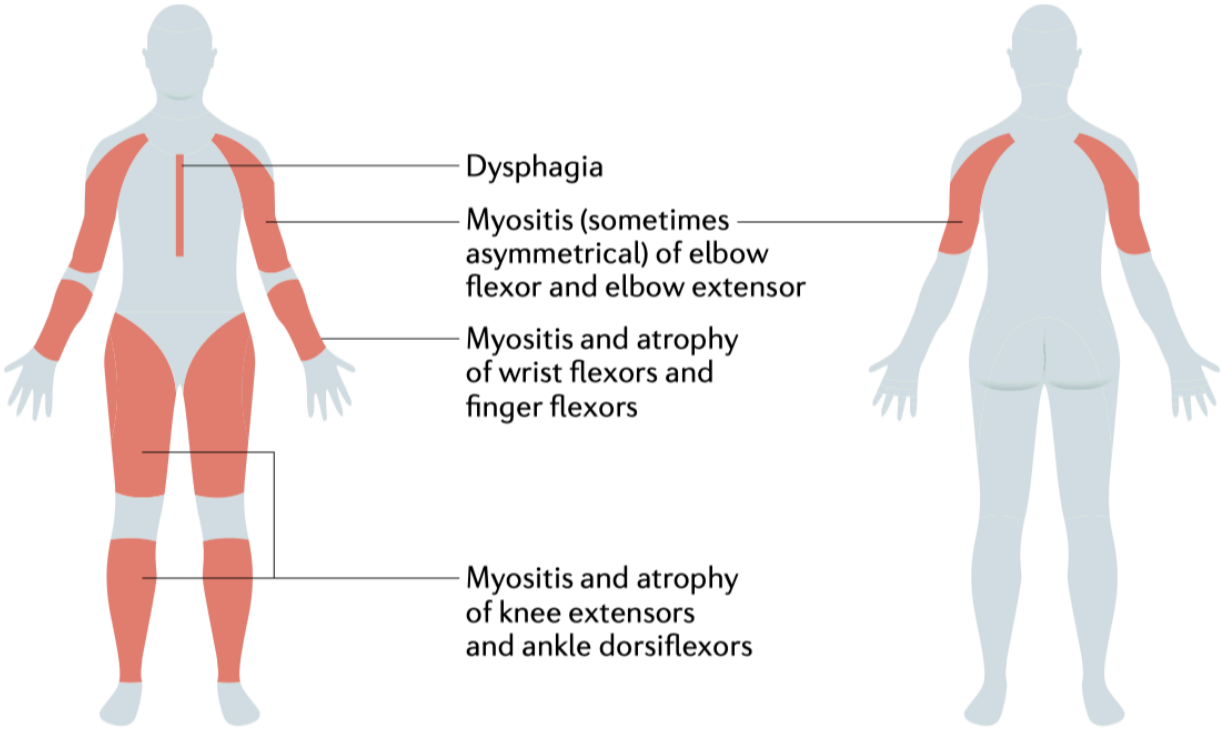

Fig. 6 | **Clinical manifestations of IBM.** Inclusion body myositis (IBM) is characterized by slowly progressive muscle weakness affecting mainly quadriceps and forearm muscles. Muscle involvement can be asymmetrical. The disease leads to substantial muscle atrophy and severe disability. Dysphagia is present in >50% of patients.

Addendum

Lundberg et al., (2021) does not mention respiratory involvement in IBM. Research indicates that respiratory failure (usually due to diaphragmatic weakness) and pneumonia (usually due to complications of dysphagia) are the most common causes of mortality in IBM patients (see Lelièvre et al., 2021; Naddaf et al., 2021).

In a small sample of IBM patients, Lelièvre et al., (2021) found that some 45 % displayed dysfunctional diaphragmatic activity.

Naddaf, E., Shelly, S., Mandrekar, J., Chamberlain, A. M., Hoffman, E. M., Ernste, F. C., & Liewluck, T. (2021). Survival and associated comorbidities in inclusion body myositis. *Rheumatology*, keab716. https://doi.org/10.1093/rheumatology/keab716

Similar to previous reports, the death in IBM patient was most commonly related to respiratory complications including respiratory failure or pneumonia.

Lelièvre, M. H., Hudson, M., Botez, S. A., & Dubé, B. P. (2021). Determinants and functional impacts of diaphragmatic involvement in patients with inclusion body myositis. Muscle & Nerve, 63(4).https://doi.org/10.1002/mus.27170

Nine patients (9/22 45%) had “low” diaphragm activity. Age, sex, body mass index, time since diagnosis of IBM and serum CK levels were not statistically different between these patients and those with “high” diaphragm activity.

Together, these findings provide new insights on the possible effects of IBM on the diaphragm and on the contribution of respiratory muscle involvement to respiratory symptoms and exercise limitation in this population. This should alert clinicians involved in the care of patients with IBM to the possibility of diaphragm weakness when confronted with symptoms of unexplained dyspnea or exercise intolerance. In addition, our results support the usefulness of ultrasonography as a clinical tool in this population, allowing a rapid, simple and non-invasive estimation of diaphragm function that is related to relevant clinical outcomes.