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EDITORIAL

Progress in inflammatory myopathies: good but not good enough

During the past decade there have been remarkable achievements in the immunopathogenesis of the inflammatory myopathies that laid the grounds for more effective therapeutic interventions. This editorial summarises where we stand today in our understanding of these disorders and their treatment, identifies key biological issues that need further study, and considers possibilities of applying new and more specific therapeutic interventions.

Classification, nomenclature, and clinical diagnostic challenges

The inflammatory myopathies comprise three major and distinct subsets: dermatomyositis (DM), polymyositis (PM), and sporadic inclusion body myositis (s-IBM) (table 1). All three have in common the presence of moderate to severe muscle weakness and endomysial inflammation, but each subset retains characteristic clinical, immunopathological, and morphological features.[1 2]

DERMATOMYOSITIS

Dermatomyositis is a distinct disease that affects muscle and skin. Involvement of the muscle results in mild to severe myopathy; involvement of the skin causes a heliotropic rash on the face and knuckles and a flat red rash on the trunk, knees, neck, chest, and back. When the muscle strength is normal, the term dermatomyositis sine myositis is used even though muscle biopsy shows the same changes as in patients with clinical signs of myositis. Dermatomyositis, but not PM or IBM, may overlap with scleroderma and mixed connective tissue disease.[1] Unique for DM is its frequent association with malignancies. Putative cancer peptides that share antigenic epitopes with the muscle or endomysial capillaries have not yet been identified.

POLYMYOSITIS

Polymyositis remains a challenge in definition and diagnosis. It is a diagnosis of exclusion and must be considered in every patient with acquired myopathy of subacute onset who does not have family history, exposure to myotoxic drugs or toxins, another acquired muscle disease caused by endocrine, metabolic or neurogenic causes, IBM, or dystrophy (table 1). Exclusion of the last two conditions is crucial because they account for most patients with the erroneous diagnosis of PM. By contrast with PM, the muscle weakness in IBM and dystrophies develops slowly (over months or years) and usually affects certain muscle groups more than others. The difficulties also arise because of the presence of endomysial inflammation, which is prominent in s-IBM and not infrequent in certain sporadically occurring dystrophies such as Duchenne's and Becker's disease, the facioscapulohumeral, scalpulohumeroperoneal, and oculopharyngeal muscular dystrophies, and in the dysferlinopathies. The finding that in these patients steroids lower the creatine kinase concentration and exert a mild clinical improvement, adds to the confusion. Very high but persisting creatine kinase concentration (above 5000 IU), especially in children and young adults, should raise the diagnostic suspicion for dystrophinopathy, sarcoglycanopathy, or dysferlinopathy and mandates the search for proper

Table 1 Inflammatory myopathies

Dermatomyositis (DM):
- Affects skin and proximal muscles. Creatine kinase is high or normal.
- Dermatomyositis sine myositis affects only, or predominantly, the skin.

Polymyositis (PM):
- Affects proximal muscles and evolves subacutely.Creatine kinase is always increased. It is a diagnosis of exclusion in a patient who does not have:
  - (*a*) family history; (*b*) exposure to myotoxic drugs or toxins; (*c*) another acquired muscle disease caused by endocrine, metabolic or neurogenic causes; (*d*) certain sporadically occurring dystrophies (dystrophinopathies, sarcoglycanopathies, dysferlinopathies); and (*e*) inclusion body myositis.

Inclusion body myositis and myopathies:
- Affect concurrently proximal and distal muscles. Disease evolves slowly (over years). Creatine kinase is normal or elevated. There are three subtypes:
  - (*a*) Sporadic inclusion body myositis (s-IBM)
    - This is an inflammatory vacuolar myositis with a distinct clinical phenotype
  - (b) Familial (inflammatory) inclusion body myositis (f-IBM)
    - This is an inflammatory vacuolar myositis with a phenotype identical to s-IBM occurring in family members of the same generation
  - (c) Hereditary, non-inflammatory, inclusion body myopathies (h-IBM)
    - These are heterogenous groups of non-inflammatory vacuolar myopathies. Two major subsets are recognised:
      - (1) Recessive inheritance with quadriceps sparing. This is a distinct disease world wide, linked to 9p1q; and
      - (2) dominant inheritance, which are still unclassified

genetic testing. The old criteria of Peter and Behan proposed in 1975[3] have served the community very well for years but they cannot exclude many of the aforementioned conditions; hence, the need to rely on the new criteria introduced since 1991.[1] It is unclear why PM is very uncommon (almost rarely seen) in children, by contrast with DM, which occurs in all ages, and why s-IBM is seen mostly in adults. Also, it is not known why DM, but not PM or IBM, is associated with cancer.

INCLUSION BODY MYOSITIS

Inclusion body myositis is the commonest of the inflammatory myopathies above the age of 50.[1 4–7] It affects men more often than women. Although it is commonly suspected when a patient with presumed PM does not respond to therapy, early involvement of finger flexors (causing difficulty holding on to objects such as golf clubs, turning on keys, or tying knots) and the quadriceps muscle resulting in frequent falls, may be clues to early clinical diagnosis.[1 4] Dysphagia and choking episodes are common, occurring in up to 60% of the patients, especially late in the disease. The distal, asymmetric, and slowly progressive weakness and atrophy may resemble a lower motor neuron disease especially when the serum creatine kinase is not raised. Three distinct subsets of IBM have now been recognised (table 1): (*a*) the sporadic IBM, an inflammatory vacuolar myositis with the distinct clinical phenotype described above; (*b*) the familial inflammatory IBM, an inflammatory vacuolar myositis occurring in several family members of the same generation with clinical and histological phenotype identical with s-IBM[8]; and (*c*) the hereditary inclusion body myopathy, a group of non-inflammatory vacuolar myopathies of recessive or dominant inheritance.[5 7] The recessive disease, characterised by quadriceps sparing, originally described in Iranian Jews, but now identified in many ethnic groups,[9] is linked to chromosome 9p1q.[10] The dominant h-IBM includes a heterogenous group of vacuolar myopathies not yet genetically identified.

LABORATORY FINDINGS

Polymyositis and up to 20% of IBM, is associated with various autoimmune disorders or autoantibodies, immunodeficiencies, connective tissue diseases, or viral infections. Polymyositis and IBM, however, do not overlap with any of those disorders as patients with DM do. The creatine kinase concentration is usually increased, not higher than 10-fold in IBM and as high as 50-fold in PM and DM, but it can be normal from the outset in some patients with DM and and those with IBM (table 1). Electromyography is useful in showing active myopathy but it does not distinguish an inflammatory myopathy from a dystrophy. The so-called "mixed potentials" are not unique to IBM and claims to the contrary should be viewed with caution.

HISTOPATHOLOGICAL CHALLENGES: WHAT IS CERTAIN AND WHAT IS NOT

Muscle biopsy can be definitive in establishing the diagnosis of DM, PM, or IBM and excludes other neuromuscular diseases.

In DM the histology is unique. The inflammation is predominantly perivascular and in the interfascicular septae. There is endothelial hyperplasia of the endomysial vessels, obliteration of capillaries that leads to ischaemia,[1 6 11] muscle fibre necrosis in a wedge-like shape or at the periphery of the fascicle, and dilatation of the lumen of the remaining capillaries to compensate for the ischaemia.[12 13] The resulting perifascicular atrophy is diagnostic for DM, even in the absence of inflammation. Perifascicular atrophy does not occur in any other disease. Some of the changes in DM need to be separated from fasciitis (eosinophilic or macrophagic). In fasciitis the endomysial vessels are normal, and the inflammation is predominantly in the fascia spilling over to the periphery of the fascicle.

In PM the cellular infiltrates are within the fascicles. In typical cases, lymphocytes initially invade non-necrotic muscle fibres resulting in phagocytosis, muscle fibre necrosis, and finally increased connective tissue. Major diagnostic challenges occur when: (*a*) there is minimal or no inflammation. In these cases, when the clinical inclusion and exclusion criteria mentioned above are met, the diagnosis of possible PM is considered, provided that the muscle enzyme histochemistry is not informative for a specific disorder and immunocytochemistry has excluded defects in any of the known proteins such as dystrophin, sarcoglycans, emerin, or dysferlin (the lack of inflammation is thought to be due to a sampling error); (*b*) there are many necrotic fibres invaded by macrophages but a few T cells, indicative of a necrotising myopathy. These cases require immunocytochemical studies to demonstrate the presence of the cytoskeletal or membrane proteins mentioned above and a good clinical history to exclude exposure to toxins; and (*c*) the inflammation is accompanied by features of a chronic myopathy (large fibres, increased connective tissue) that resembles IBM, but without the vacuoles.[12] In these patients, the possibility of IBM should be kept in mind and, if there is no adequate response to treatment, a repeat muscle biopsy should be considered.

In s-IBM the histological hallmarks are basophilic granular inclusions distributed around the edge of slit-like vacuoles (rimmed vacuoles); primary endomysial inflammation with T cells invading non-necrotic muscle fibres in a pattern identical with PM; tiny deposits of Congo red or crystal violet positive amyloid within or next to some vacuoles; abnormal mitochondria seen as ragged-red and cytochrome oxidase negative fibres that contain mitochondrial DNA deletions; and characteristic tubulofilamentous inclusions within the cytoplasm or myonuclei.[1 4 5 7 13 14] Demonstration of the filaments by electron microscopy may not be essential for the diagnosis of IBM, if all the other characteristic features including amyloid deposits are fulfilled. Further, such filaments are not unique to IBM; they can be seen in other vacuolar myopathies, even in vacuoles seen in chronic neurogenic muscles such as old polio.[15] If inflammation is absent but the clinical phenotype is typical of s-IBM, the diagnosis of probable IBM is considered.[12] In a patient with family history of a recessive disease the histology of non-inflammatory vacuolar myopathy suggests hereditary inclusion body myopathy and raises the need to pursue linkage studies to chromosome 9p. In all other cases, the term vacuolar myopathy should remain until further clarification.

Pathogenesis: what we do know and what we need to know

IMMUNOPATHOLOGY OF DERMATOMYOSITIS

In DM the disease seems to begin with activation of the complement that forms C3b and C4b fragments, which leads to the formation and deposition of MAC on the endomysial microvasculature.[16] The deposition of MAC causes osmotic lysis of the endothelial cells and capillary necrosis resulting in ischaemia, microinfarcts, inflammation, endofascicular hypoperfusion, and finally perifascicular atrophy.[6 11 13 16 17] Cytokines induced by activation of complement, upregulate the expression of the adhesion molecule L-selectin and integrins LFA-1 and VLA-4 on leucocytes and their respective ligands GlyCAM-I, ICAM-I, and VCAM-I on the endothelial cells and facilitate the transmigration of activated cells.[6 11 18 19] The inflammatory cells in the perimysial and perivascular

regions are mostly B cells and CD4+ cells, suggesting involvement of humoral mediated mechanisms.[6 11 17] Some uncertainties exist. What triggers complement activation? Do the endomysial B cells produce antibodies? If so, what is the target antigen? Is there a role for T cell mediated cytotoxicity? Does the triggering agent recognise common antigens in skin and muscle that explain their concurrent involvement? What factors (cytokines, transforming growth factor-β (TGF-β),[20] other?) drive the excessive fibrosis seen in the disease? What triggers the formation of calcinosis?

IMMUNOPATHOLOGY OF POLYMYOSITIS AND INCLUSION BODY MYOSITIS

Cytotoxic T cells

In PM and IBM, there seems to be an antigen directed and MHC I restricted cytotoxicity mediated by cytotoxic CD8+T cells,[1 6 11 17] as supported by the following: (*a*) cell lines established from muscle biopsies exert cytotoxicity to autologous myotubes; (b) CD8+ cells send spike-like processes into non-necrotic muscle fibres and traverse the basal lamina; (c) the autoinvasive CD8+ T cells contain perforin and granzyme granules which are directed towards the surface of the fibres and on their release induce cell death through necrosis, but not apoptosis; (*d*) there is clonal expansion of T cells with restricted usage of TCR variable region of certain TCR gene families, indicative of an antigen driven T cell response[2 21 22 23]; (*e*) the clonally expanded T cells invade muscle fibres expressing MHC I class antigen,[13] a prerequisite for antigen recognition by the CD8+ cells; (*f*) muscle fibres express the costimulatory molecule BB1, make cell to cell contact with their CTLA-4 and CD28 ligands on the autoinvasive CD8+ T cells and behave like antigen presenting cells.[24 25]

Some missing links need to be identified. What is the nature of the antigenic peptide bound by the MHC I for presentation to CD8+ T cells? Is this an endogenous self protein synthesised within the muscle fibre or is it an endogenous peptide—that is, a virus? Although the failure to amplify viruses within the muscle fibres[11] may seem to be against a viral hypothesis, it does not exclude viruses that "hit and run". Is the inflammation in IBM primary as the immunopathology indicates, or secondary due to other IBM associated local reactions discussed later? Why does IBM not respond to immunotherapies[26] even though the endomysial T cells have the same activation markers as in PM?

Cytokines and adhesion molecules

Cytokines derived from T cells (interleukin-2 (IL-2), IL-4, IL-5, and INF-γ), cytokines derived from macrophages (IL-1, IL-6, and (tumour necrosis factor-α (TNF-α)), and cytokines that are derived from either, such as GM-CSF and TGF-β, have been variably amplified in the muscles of patients with PM and IBM.[2 11 18 19] Matrix metalloproteinases MMP-2 and MMP-9,[27] adhesion molecules L-selectin and integrins LFA-1, VLA-4 and their respective ligands ClyCAM, ICAM-1, and V-CAM-I, are upregulated on the T cells, endothelial cells, or muscle fibre membrane and enhance T cell attachment and migration.[2 18 19] Whether cytokines also exert a direct myocytotoxic effect is unclear. In vitro, IL-I and TNF-α are toxic to the myotubes and MMP-2 and IL-1β enhance amyloid formation[2] but we do not know if they also exert a similar effect in vivo.

Association with viral infections

Although viruses have been indirectly associated with myositis, molecular techniques have not proved their presence. The best evidence for a viral connection has been with retroviruses. Monkeys infected with the simian immunodeficiency virus and humans infected with HIV and HTLV I develop PM or IBM either as an isolated clinical phenomenon or concurrently with other manifestations of AIDS.[1 11 28] Viral antigens or viral RNA are not detected within the muscle fibres, indicating absence of persistent infection or viral replication. In HIV-1 and HTLV-1 PM and IBM, the autoinvasive CD_8+ T cells are not virus specific but they are cytotoxic, having the same activation markers as the T cells in retroviral negative PM and IBM.[11 28] Some endomysial macrophages harbour retroviral antigens and may enhance local pathology via the release of cytokines, especially TNF-α. If other viruses trigger PM or IBM, as they probably do based on the retroviral experience, we need to know: (*a*) Which virus? (*b*) What is its receptor on muscle fibre? (*c*) Does it "hit and run" inducing an autoimmune attack, or does it incorporate into the genome and change the cell cycle to produce faulty antigenic muscle peptide? (*d*) The aB crystalline upregulation, recently noted in the healthy fibres of IBM muscles as an upstream stressor effect,[29] may be either related to such a viral insult or it represents a non-specific stress autoantigen. Time will tell.

Non-immune factors in s-IBM: amyloid and vacuoles

In s-IBM, there are amyloid deposits within some vacuolated muscle fibres accompanied by various amyloid related proteins including β-APP, chymothrypsin, apoE, or phosphorylated tau.[5 7 14] The origin and role of amyloid in s-IBM remain unclear. Is the amyloid secondary, related to chronicity of the disease and the persistent chronic inflammation, or is it primarily generated de novo? A link between b-APP and inflammation may be via IL-1 and MMP-2, both of which are upregulated on the amyloid deposits.[2 27] In IBM, the noted excess of IL-1β may be derived not only from the abundant endomysial macrophages and T cells but also by the β-APP, which is a known enhancer of IL-1β production. In turn, IL-1β upregulates β-APP and β-APP gene expression and closes the loop, as follows: IL-1β→β-APP→IL-1β→inflammation.[2] Treatment trials with agents that deplete inflammation or break the amyloid deposits may tell us which of the two is the main culprit in IBM.

Another mystery in IBM is the vacuole. Why and how are they formed and increase with disease progression? Within the vacuolated muscle fibres, there is increased activity of the P42 mitogen activated protein kinase, indicating abnormal intracellular protein phosphorylation.[30] But, it is unclear if this is primary and enhances T cell activation and vacuolar formation or is secondary due to ongoing vacuolar degeneration.

Immunotherapies: the present

Although the immunosuppressive therapies in DM and PM are not antigen specific, they induce significant improvement in most of the patients for a period. The following are currently used:

STEROIDS AND IMMUNOSUPPRESSANT DRUGS

There is no doubt, based on empirical experience, that steroids provide modest to dramatic improvement in most patients with bonafide PM and DM, but do not help IBM. Azathioprine, methotrexate, or cyclosporin offer varying degrees of steroid sparing effect and a mild to modest additional benefit in some patients.[31]

INTRAVENOUS IMMUNOGLOBULIN

Based on a controlled trial, treatment with high dose IVIg has shown impressive improvement in patients with DM.[32] In PM the results are also very promising.[31] Three controlled trials[32–34] have shown that IVIg does not offer a statistically significant improvement in IBM, but a third of the

patients experience transient benefit. When combined with prednisone there is no added benefit.[34] Because IVIg is the only drug that shows some help, it can be tried for 2 or 3 months in those patients who exhibit significant life threatening dysphagia or rapid worsening.

NEW, READY TO USE IMMUNOSUPPRESSANT DRUGS

Sirolimus (Rapamycin), mycophenolate mofetil, and FK506 (Tacrolimus), are new agents that seem to benefit difficult cases, as discussed below.

THE GOALS OF THERAPY AND THE CURRENT, STEP BY STEP, THERAPEUTIC PRACTICE

The practical goals of therapy in PM and DM are to improve function in the activities of daily living and improve muscle strength. In essence, the therapy is also designed to induce a remission of the dysimmune state or to minimise muscle fibre loss. Although when the muscle strength improves, the serum creatine kinase concentration tends to fall concurrently, the reverse is not always true because most of the immunosuppressive therapies can result in a decrease in serum muscle enzymes without necessarily improving muscle strength. Based on uncontrolled, empirical, and controlled trials conducted in PM, DM, and IBM and until further control trials are completed, the following step by step empirical approach is now followed in the treatment of patients with PM and DM:

Step 1

High dose corticosteroids orally (or, at times, intermittently intravenously). The concurrent use of azathioprine or methotrexate from the outset is optional and practised by a few. It is not currently my practice.

Step 2

If step 1 is not satisfactory, add a mild immunosuppressant, such as azathioprine or methotrexate, or start IVIg. My current practice is to go directly to IVIg before considering azathioprine or methotrexate.

Step 3

If step 2 fails, consider mycophenolate, cyclosporin, or cyclophosphamide

For IBM, treatment decisions are difficult. If mild, we may do nothing or add low dose steroids combined with CoQ10 and an exercise programme. If the disease is rapidly worsening and dysphagia is life threatening, we try IVIg. The value of mycophenolate has not been studied.

Semispecific immunotherapy: 2000 and beyond

As we have entered 2000, more rational, therapeutic approaches can be applied, taking advantage of the progress in molecular immunology.

BLOCKADE OF THE SIGNAL TRANSDUCTION IN T LYMPHOCYTES

Selective inhibition of TCR signalling pathways induces selective immunosuppression. On TCR ligation, there is activation of several tyrosin kinases, which leads to transcriptional activation of the cytoplasmic serine phosphatase calcineurin.[35] Calcineurin leads to activation of IL-2 promoter. Two immunosuppressive drugs FK506 and cyclosporin inhibit the calcineurin phosphatase activity[35] and seem promising in difficult cases. Rapamycin, which acts via a calcineurin independent pathway to prevent the translation of mRNA for key cytokines, is another promising drug. Further, the costimulatory molecules CD28 and CTLA-4, which are upregulated in PM and IBM,[24 25] may become specific targets for immunotherapy. The currently available monoclonal antibodies against CD28/CTLA-4 which induce anergy by blocking costimulation may be considered.

AGENTS AGAINST IMMUNOMODULATING CYTOKINES

Anti-TNF-a strategies

TNF-a is not only upregulated in vivo in PM and IBM muscle but it is also toxic to myotubes in vitro. The currently available monoclonal antibodies against TNF-a may be considered for future trials.

β- Interferons

These agents, currently used in multiple sclerosis, may also be applicable for trials in inflammatory myopathies.

AGENTS AGAINST ADHESION MOLECULES AND RECEPTORS (ANTICELLULAR "GLUES")

Matrix metalloproteinases

These are endopeptidases that play a fundamental part in T cell attachment to the endothelial cell wall and muscle fibres. Among them, MMP-2 and MMP-9 are upregulated in PM and IBM muscles.[27] Currently available drugs that block the activity of MMPs may be considered for future trials.

Integrins and their receptors

Integrins integrate the activation of extracellular matrix and cytoskeleton and facilitate the communication of cell to cell and cell to matrix. Among them, β2 integrins/VCAM receptors, β1 integrins/ICAM-1, and α2 and β4 integrins/FA-1, are upregulated in PM, DM, and IBM muscles and facilitate T cell transport across the blood vessel wall.[36] Available agents against integrins and their receptors may be considered in future trials.

Prognosis: good but we need better

Dermatomyositis responds more favourably to therapy than PM. Overall, most patients improve, and many of them make a full functional recovery, which is sustained with maintenance therapy. However, up to 30% of the patients may be left with residual muscle weakness. The 5 year survival rate for treated patients with PM and DM is now approaching 80%. On the other hand, IBM is predictably disabling. Most of these patients will require use of an assistive device such as a cane, walker, or wheelchair. The older the age of onset, the more rapidly progressive the course of IBM seems to be.[37] As this disabling disease is now more easily recognised, the need for aggressive therapies to halt progression is urgent.

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