

Topical Reviews

An overview of current research and practice in rheumatic disease



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IDIOPATHIC INFLAMMATORY MYOPATHIES

Wilhelmina MH Behan

Professor of Muscle Pathology
 University of Glasgow

Roger D Sturrock

McLeod/arc Professor of Rheumatology
 University of Glasgow

- **The idiopathic inflammatory myopathies (IIM) are rare but potentially treatable diseases**
- **Their chief feature is muscle weakness, usually proximal, painless and of insidious onset**
- **Muscle biopsy is diagnostic, revealing necrosis of HLA I antigen-positive fibres, mononuclear cell infiltrates and regeneration**
- **There are three main subgroups: dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM)**
- **In all three the aetiology appears to be immune-mediated: in DM, humoral, in PM and in IBM, cell-mediated**
- **In IBM additional degenerative features are found which resemble those in Alzheimer's disease**

INTRODUCTION

The idiopathic inflammatory myopathies (IIM), or myositis, are rare disorders with a combined incidence difficult to determine but probably in the region of 15 per million population.^{1,2} Diagnosis is important since there is significant morbidity and mortality in the absence of treatment, but it may be difficult because of the insidious onset of the characteristic muscle weakness. There are three main subgroups, dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM), which differ in aspects of their clinical and pathological features and their pathogenesis.¹⁻⁴ They each may present in isolation or with a connective tissue disorder (systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome, polyarteritis nodosa (PAN), scleroderma and mixed connective tissue disease (MCTD)), their clinical and pathological features, however, remaining true to type.

The differential diagnosis includes eosinophilic, nodular or focal myositis, the vasculitides, the recently described macrophagic myofasciitis (which occurs at the site of vaccine depot immunisations), and a late effect of chronic graft versus host disease.^{1,5-8} Inflammatory myopathies may also be caused by toxins, drugs and infectious agents (viral, bacterial, parasitic and fungal),⁵ the three latter being reported more commonly since the advent of the acquired immunodeficiency syndrome.

Numerous viruses have, at one time or another, been postulated as causative agents for IIM but none has been confirmed.^{5,9,10} Coxsackie viruses appeared originally to be strong candidates but are not detected in muscle biopsies, even in the earliest cases.¹⁰ The human

immunodeficiency virus and other retroviruses may be associated with the typical clinical and pathological features of PM but direct infection is not the cause.¹¹

The diagnosis of IIM depends on clinical examination, electrophysiological data, serum muscle enzyme levels, various autoantibodies and muscle biopsy.¹² The clinical features are described in excellent recent reviews.^{1-3,12}

GENERAL FEATURES

TABLE 1. Evidence for an antigen-specific response in idiopathic inflammatory myopathies.

- Activated cytotoxic T-cells invade apparently healthy muscle fibres
- Undamaged fibres express MHC I and costimulatory molecules
- Clonal restriction of TCR repertoire
- In DM, complement component deposition in microvessels

MHC major histocompatibility complex; DM dermatomyositis; TCR T-cell receptor

In all three subgroups, DM, PM and IBM, immune mechanisms have been demonstrated. Association with almost every autoimmune disease has been described and there is over-representation of human leucocyte antigen (HLA) DR3, especially in certain antibody-associated subsets of DM.^{1-3,13-15} Tissue-specific (antinuclear, rheumatoid factor, antimuscle and anti-thyroid) myositis-associated and myositis-specific autoantibodies occur.¹⁵ The myositis-specific group is the most useful in diagnosis. It includes six autoantibodies directed at the aminoacyl transfer ribonucleic acid (tRNA) synthetases, a group of enzymes which attach tRNAs to the corresponding amino acid. Anti-Jo-1, to histidyl tRNA synthetase, is the most common, and characterises a specific subset of younger patients with interstitial lung disease, arthritis and Raynaud's syndrome.¹⁶ The reason why these enzymes is targeted is not known. Molecular mimicry has been suggested but these high affinity enzymes can exist in complexes with the substrate tRNAs and the antibodies may represent epitope spreading to another macromolecular complex.¹⁵

Another myositis-specific autoantibody is directed at the Mi-2 antigen which acts in chromosomally mediated regulation of transcription,¹⁵ while a novel antibody to the signal recognition pathway and its membrane-associated receptor (or docking) protein has been described in a subset of unusually severe and progressive DM.¹⁷ Such an antibody could inhibit the targeting of nascent secretory and membrane proteins to the protein translocation apparatus of the endoplasmic reticulum. Recent studies have suggested that antigen

cleavage during apoptosis, particularly by granzyme B, may be an important factor¹⁵ in inducing these autoantibodies. The significance of these antibodies to intracellular antigens in causing tissue damage is, however, uncertain.

The reason for the documented association with certain malignancies in IIM is quite unknown but there is no doubt that DM is strongly associated with a wide range of cancers (SIR 3.0, 95% CL 2.5-3.6) – particularly ovarian, lung, pancreatic, stomach and colorectal, and non-Hodgkin's lymphoma – while PM is linked to an increased risk of non-Hodgkin's lymphoma and lung and bladder cancers.^{18,19} The risk of malignant disease is highest at time of diagnosis but remains for up to 5 years in DM, except in juvenile DM where it is very rare. The tumours may vary in different racial groups, e.g. nasopharyngeal carcinomas are found in Taiwanese.¹⁸ The increased risk emphasises the diagnostic work-up necessary in patients under the care of a rheumatologist, dermatologist or neurologist. Patients presenting to a general physician with signs of malignancy and who are then noted to have DM or PM do not pose the same problem.²⁰ Since no clinical or pathological tests will distinguish between IIM with or without malignancy, it has been suggested that clinical examination and routine laboratory screening should be followed by appropriate body scan and endoscopic evaluation of upper and lower gastrointestinal tract.²⁰

PATHOGENESIS

Muscle biopsy is mandatory for diagnosis,^{12,21} and it affords us major insights into pathogenesis based on the features summarised below. Needle muscle biopsy from the vastus lateralis or biceps brachii muscles is appropriate.

Pathology

Muscle fibre damage and inflammation are the hallmarks of DM, PM and IBM with the three subgroups showing variation in location, degree and associated features.^{4,21,22} They can be summarised as follows. In DM fibre necrosis is seen singly, in small groups of 4–5 (microinfarcts), or in ribbons up to 10 thick, at the periphery of the fascicle. In PM and IBM, however, fibre necrosis – again single or in small clusters – is seen scattered throughout the fascicle.

An inflammatory infiltrate is present at perivascular, perimysial and endomysial sites, again with variation: it is least obvious or absent in DM, while it is more common in IBM and conspicuous in PM. Analysis of the mononuclear cells reveals that a mixed infiltrate of T- and B-cells and macrophages with very few K/NK (killer/natural killer) cells is present. B-cells and

T-helper cells predominate at all sites in DM, whereas in PM and IBM activated cytotoxic T-cells are found in large numbers. The elegant studies of Engel and Arahata first revealed that it is non-necrotic, i.e. apparently healthy, fibres which can be seen undergoing invasion by these T-lymphocytes in the latter two disorders.²²

Blood vessel changes are seen in DM but rarely in PM or IBM: these consist of endothelial swelling and hyperplasia in endomysial capillaries and are associated with necrosis (microinfarcts). Complement components have been demonstrated in these blood vessels (see below).

TABLE 2. Inclusion body myositis: inclusion bodies and vacuoles present in muscle fibres.

Inclusion bodies	
•	βA fibrils and phosphorylated τ paired helical filaments
•	βAPP, βA
•	Cholesterol, LDL-receptors and caveolin-1
•	Prion protein
•	Presenilin-1, α-synuclein (typical of Alzheimer's disease)
•	AChR
Vacuoles	
•	Fragments of degraded protein

AChR acetylcholine receptor; βA β-amyloid; βAPP β-amyloid precursor protein; LDL low-density lipoprotein

In IBM rare but distinctive features have become better appreciated since frozen sections superseded the paraffin preparations on which they were difficult to detect. They consist of vacuoles and eosinophilic inclusion bodies in the fibres.^{4,23} The vacuoles contain membranous debris only but the inclusions have an array of constituents, including β-amyloid precursor protein (βAPP), ubiquitin, apolipoprotein E (APOE), phosphorylated τ and prion protein, as discussed below.

The cellular infiltrate

This is a major diagnostic feature and a main factor in pathogenesis. T-cells are predominant in the inflammatory infiltrate of PM and IBM and, of great interest, can be shown invading fibres which are apparently healthy.²² At these sites they are cytotoxic, activated and associated with macrophages, suggesting a specific T-cell-mediated attack. This view is supported by evidence of consistently strong fibre expression of major histocompatibility (MHC) antigens.^{24,25} Normal muscle fibres, unless they are regenerating, do not express Class I (or II) antigens but, as stated, widespread expression is seen in IIM, particularly in apparently healthy (i.e. non-necrotic) fibres undergoing invasion.

MHC I expression on target cells is a prerequisite for antigen-specific T-cell-mediated cytotoxicity. It was important to see if muscle fibres showed this expression as a prime event or only because of interferons released from the inflammatory infiltrate. Several workers have shown that there is no relationship between increased expression and local interferon synthesis by mononuclear cells.^{24–26} It appears therefore that Class I and II molecules could be primary factors in initiating and maintaining fibre damage. That this is indeed the case is suggested by the work of Nagaraju et al,²⁷ who used a controllable, muscle-specific promoter system to upregulate MHC I in the skeletal muscles of young mice. The mice developed an inflammatory myopathy with clinical, biochemical, histological and immunological features similar to human myositis. It appeared therefore that an autoimmune myopathy could result from the sustained upregulation of MHC I, depending not on the specificity of the stimulus but on its context, location and duration.²⁷ Other workers have confirmed that upregulation of MHC I antigens may prolong muscle damage and slow regeneration.²⁸ The increased expression of HLA-G, a non-classical MHC I antigen with other important immune reactions, which is also seen in IIM, may play a role.²⁹

Costimulatory molecules

For the complete activation of the T-cell, engagement of the T-cell receptor (TCR) – not only with MHC, but also with a costimulatory signal – is needed. The CD28/B7 receptor/ligand system is one of the dominant co-stimulatory pathways and expression of the co-stimulatory molecule BB1 and its counter-receptor has been found in IIM, with MHC I⁺, BB1⁺ fibres binding to their receptors on autoinvasive CD8⁺ cells.³⁰ CD40, another costimulatory molecule, has also recently been reported on the cell surface of muscle fibres in IIM, with its ligand, CD40L, expressed on the infiltrating mononuclear cells.³¹ There appears to be no doubt therefore that T-cells contribute to the damage in IIM.

Clonal restriction of T-cells

Another way to confirm that the attack is antigen-specific is to look for clonal restriction in the T-cell infiltrate. A strikingly limited TCR repertoire has indeed been shown.^{32–35} Molecular characterisation of muscle-infiltrating lymphocytes in PM revealed a variety of rearranged variable Vα/β TCRs, with Vα1, Vα5, Vβ1 and Vβ15 being the most common (in 60–100% of Vα/β TCRs) and sequence analysis showing the Tβ2.1 region in 90% of the Vβ15 clones studied.³² In patients with anti-Jo-1 antibodies the findings indicated that in DM the TCR repertoire was predominantly polyclonal but in PM it was oligoclonal.³³ In all three subgroups it

appears that there is clonal expansion of autoaggressive CD8⁺ T-cells with a strikingly limited TCR repertoire, and the same clones persist during the course of the disease.^{34,35} The TCR usage of autoinvasive and interstitial T-cells is not the same.

The α/β TCR appears to be the one invariably involved. Only one case has been reported in which γ/δ T-cells invaded non-necrotic muscle fibres in a patient with PM, the fibres being highly reactive for 65 kd heat shock protein.³⁶

Other cytotoxic mechanisms

Other cytotoxic mechanisms have been considered in IIM and abundant perforin-expressing activated helper and cytotoxic T-cells have been found in PM and DM. There was a striking difference in the intracellular localisation of perforin. In DM it was randomly distributed in T-cell cytoplasm in keeping with non-specific activation. In PM, however, it was obviously directed towards the target muscle fibre surface where the vectorial orientation indicated specific recognition by the T-cell of surface antigen on the non-necrotic muscle fibres followed by a perforin-and-secretion-dependent mechanism of injury.³⁷

Fas/Fas ligand interaction can act as a mechanism for T-cell cytotoxicity as well as inducing apoptosis. There is upregulation of Fas on muscle fibres in IIM, but it is mainly on regenerating fibres and therefore more likely to be part of the developmental programme for gene expression.³⁸ Apoptosis does not appear to be of significance in these disorders.³⁹

Cytokines

Cytokines were initially thought to play a major role in the immune damage by inducing MHC I expression on muscle fibres but, as already discussed, this is an independent occurrence: both MHC I and MHC II expression are quite unrelated to the inflammatory infiltrate.²⁴⁻²⁶ Proinflammatory (IL-1 α and IL-1 β , TNF α) and macrophage inflammatory proteins 1 α (MIP-1 α) as well as inhibitory cytokines, e.g. transforming growth factor (TGF β), have been sought.⁴⁰ There is no doubt that TNF α is present, especially in juvenile dermatomyositis where a particular polymorphism (TNF α -308A) may be associated with prolonged disease.⁴¹ Monocyte chemoattractant protein 1 (MCP-1) may be strongly expressed on invading T-cells and the subset of macrophages attacking non-necrotic muscle fibres.⁴²

The cytokine studies do suggest that the endomysial capillaries are a prime target in all three IIM, with increased expression of IL-1 α , adhesion molecules and MCP-1 consistently present.⁴²⁻⁴⁴ The molecular changes in blood vessels as well as muscle fibres, however,

appear to be independent of the adjacent inflammatory infiltrates.⁴⁴

Humoral factors

In DM the major tissue injury appears to be due to humoral mechanisms. Patients with active DM have high serum levels of complement fragments, including the membranolytic attack complex (MAC), and may have antiendothelial cell antibodies.⁵ MAC and the immune-complex specific C36NEO fragment are deposited in the endomysial capillaries, leading to capillary necrosis and loss and accounting for the microinfarcts. This process is accompanied by the release of cytokines which upregulate the expression of the cell adhesion molecules VCAM-1 and ICAM-1 on the endothelial cells, which then act as ligands for leucocyte integrins which permit the adherence and exiting of activated lymphocytes to muscle fibres.⁴⁴ The loss of capillaries in muscle is actually demonstrable in vivo where ³¹P nuclear magnetic resonance spectroscopy and quantitative magnetic resonance imaging (MRI) reveal reduced oxidative phosphorylation and proton efflux.⁴⁵ It was concluded from this study that the mitochondrial changes seen occasionally in muscle biopsies in IIM are unlikely to be the primary cause of any aerobic deficit. The vascular changes in PM and IBM may be similar to those in DM but they are minor.

Inclusion bodies

IBM has attracted a great deal of attention recently because, in addition to convincing evidence of immune mechanisms similar to those in PM, the findings also point to other damage previously demonstrated only in the brain.^{4,23} Askanas and Engel analysed the inclusion bodies. They identified the chief constituent as β -amyloid (β A). On electron microscopy two structural types were seen: a rounded, plaque-like body containing β A (6–10 nm fibrils) and a linear body consisting mainly of phosphorylated τ (15–21 nm paired helical filaments). Associated with them were abnormal protein accumulations typical of Alzheimer's disease: β A protein, β APP, α -synuclein, presenilin, APOE and ubiquitin, as well as prion protein and acetylcholine receptor (AChR).²³

Could the appearance of these inclusion bodies be the initiating event in IBM, leading to immunological damage? Primary muscle cultures from patients with IBM will develop inclusions, especially if innervated in vitro.²³ Gene transduction of β APP into normal muscle cells in culture leads to myotube vacuolation and inclusion body formation.²³ Transgenic mice with overexpression of β APP develop a vacuolar myopathy – only, however, in old age.²³

Increased levels of messenger ribonucleic acid encoding β APP, prion protein and AChR have been reported, consistent with local overproduction.²³ Variants of genes encoding β APP and prion protein have been described in Alzheimer's and Creutzfeldt-Jakob diseases where these proteins are deposited in abnormal amounts, but they have not been shown in IBM – nor is a polymorphic variant of the APOE gene $\epsilon 4$ increased in IBM, as it is in Alzheimer's disease.

Askanas and Engel have proposed a hypothesis to account for the changes in IBM: overexpression of β APP with aggregation and misfolding of its proteolytic fragment, βA , as the initial event. Accumulations of phosphorylated τ and other Alzheimer-related proteins follow, accompanied by deposition of cholesterol and low-density lipoprotein receptors, all in the context of oxidative stress and muscle cell aging.²³

Expression profiles

A preliminary study of the molecular profiles in IIM has revealed that the subsets have distinct gene expression signatures based on upregulation of specific sets of immune-related genes. Both differential expression of cytokines, MHC Classes I and II, granzymes and adhesion molecules, and increased expression of actin skeleton genes, have been found.⁴⁶ In addition, novel genes which may also contribute to pathogenesis have been reported recently.⁴⁷

CLINICAL FEATURES

Idiopathic inflammatory muscle disease occurs more commonly in women with a female to male ratio of 2:1. The average age of onset is 40 years. Classification criteria for PM and DM have been produced by Mastaglia and Phillips² and are reproduced in Table 3.

Patients with DM present with a typical violaceous rash which appears over the face and upper trunk and is often associated with periorbital oedema and a heliotrope rash on the eyelids. There is periungual erythema and often red or violaceous papules (Gottron's papules) over the dorsal aspects of the interphalangeal, metacarpophalangeal, elbow and knee joints. The characteristic 'shawl sign' is the occurrence of the rash over the shoulders, upper arms and back. The rash develops early in the disease in 30–60% of patients. Although subcutaneous calcification is a major feature of DM in children this is a rare occurrence in adults.

Non-dermatological features are commonly fatigue, low-grade fever, proximal muscle weakness, dysphagia and dysphonia. Less common are symptoms and signs of heart failure (cardiomyopathy) and breathlessness due to respiratory muscle weakness or interstitial lung

TABLE 3. Classification of polymyositis and dermatomyositis.²

I	Dermatomyositis Juvenile Adult
II	Polymyositis T-cell mediated (α/β , γ/δ) Eosinophilic Granulomatous
III	Overlap syndromes With polymyositis With dermatomyositis With inclusion body myositis
IV	Cancer-associated myositis
V	Inclusion body myositis
VI	Other forms <i>Focal</i> : orbital myositis; localised nodular myositis; inflammatory pseudotumour <i>Diffuse</i> : macrophagic myofasciitis; necrotising myopathy with pipestem capillaries; infantile myositis

disease. Weight loss may be a prominent symptom in patients with underlying malignancy, and muscle atrophy occurs in established disease.

Myositis also occurs in other connective tissue diseases such as MCTD, scleroderma, SLE and PAN and more rarely in RA and Sjögren's syndrome.

IBM presents in the middle-aged and elderly and more commonly occurs in men. It predominantly targets the quadriceps muscles as well as the flexor muscles of the fingers. Dysphagia is common but disease progression is generally slow.

INVESTIGATIONS

The standard set of investigations must include chest x-ray, full blood count and erythrocyte sedimentation rate, creatine phosphokinase (CPK), alanine transferase and aspartate transaminase. An electrocardiogram should be performed and, in cases where cardiac and respiratory involvement are suspected, an echocardiogram and pulmonary function tests should be carried out. The antinuclear antibody test is positive in approximately 80% of cases with a connective tissue overlap. Other autoantibodies which may be positive are Jo-1 (20% of cases) and other extractable nuclear antibodies.

Imaging such as MRI may show muscle oedema in active myositis. Ultrasound imaging of muscle can also show areas of increased echogenicity in active muscle inflammation.

An electromyogram will be abnormal in most cases but the definitive diagnosis is made by muscle biopsy (see above).

TREATMENT

- Rehabilitation and physiotherapy are important in the treatment of myositis but drug therapy requires to be used early in the disease process.
- Steroid therapy is the cornerstone of treatment for myositis and is usually commenced at a dosage range of 30–60 mg for 2–3 months. The dosage is then gradually reduced with clinical response being judged by an assessment of muscle power and a fall and normalisation of the CPK levels. Intravenous methylprednisolone is indicated in patients with rapid and progressive onset and in patients with severe pulmonary and cardiac complications.
- Patients who are resistant to steroids or who relapse with reduction of steroid dosage will require immunosuppressive therapy. The most commonly used agents are methotrexate and azathioprine, either singly or in combination. Resistant cases may require cyclosporin or cyclophosphamide. Alternative drugs such as tacrolimus and mycophenolate may also be used in patients with a poor response.
- Intravenous immunoglobulin (IVIG) infusions at doses of 2 g/kg given monthly have been shown to be of modest clinical benefit and are useful in patients who relapse on standard therapy or where there are contraindications to prolonged cytotoxic drug treatment. The precise mechanism of action is not known but blockade of Fc receptors is important. Plasma exchange has a variable effect and is generally unhelpful. Treatment with anti-TNF blocking agents may be of benefit as there are anecdotal reports of benefit in small numbers of patients.

TABLE 4. Treatment of idiopathic inflammatory myopathies.

- Corticosteroids remain the basis of treatment
- Immunosuppressive drugs such as methotrexate and azathioprine are useful steroid sparing agents
- IVIG infusions are a useful adjunct to therapy
- Drugs such as cyclophosphamide, cyclosporine, mycophenolate and tacrolimus can be used in resistant cases

IVIG intravenous immunoglobulin

IBM is difficult to treat and does not respond well to either steroids or IVIG. Immunosuppressive therapy is worth trying in individual cases. A comprehensive review of treatment of myositis may be found in the November 2002 issue of *Rheumatic Disease Clinics of North America*.⁴⁸

PROGNOSIS

The prospect for long-term survival in myositis is good in younger patients, with a 5-year survival rate of 95%.⁴⁹ Older patients with underlying malignancy do not do as well and features such as lung, cardiac and oesophageal involvement are associated with a poor prognosis.

CONCLUSION

Immune mechanisms dominate the pathogenesis of IIM. In spite of evidence that these are antigen-specific, however, no antigens have ever been identified. In IBM the features suggest that other factors may start the process, and in DM and PM modulation by environmental agents is likely. Upregulation of immune genes and the resulting pathogenetic cascade in IIM may not be a response to foreign or self-antigens but rather may be due to a different initiating event.

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Multimedia Challenges in Rheumatology

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System requirements

IBM-PC-compatible with Pentium processor or equivalent; Microsoft Windows 95/98/ME/NT/2000/XP; CD-ROM drive; Display resolution – at least 800 x 600; Sound card and external speakers.

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