Polymyositis and dermatomyositis

Marinos C Dalakas, Reinhard Hohlfeld

The inflammatory myopathies, commonly described as idiopathic, are the largest group of acquired and potentially treatable myopathies. On the basis of unique clinical, histopathological, immunological, and demographic features, they can be differentiated into three major and distinct subsets: dermatomyositis, polymyositis, and inclusion-body myositis. Use of new diagnostic criteria is essential to discriminate between them and to exclude other disorders. Dermatomyositis is a microangiopathy affecting skin and muscle; activation and deposition of complement causes lysis of endomysial capillaries and muscle ischaemia. In polymyositis and inclusion-body myositis, clonally expanded CD8-positive cytotoxic T cells invade muscle fibres that express MHC class I antigens, which leads to fibre necrosis via the perforin pathway. In inclusion-body myositis, vacuolar formation with amyloid deposits coexists with the immunological features. The causative autoantigen has not yet been identified. Upregulated vascular-cell adhesion molecule, intercellular adhesion molecule, chemokines, and their receptors promote T-cell transgression, and various cytokines increase the immunopathological process. Early initiation of therapy is essential, since both polymyositis and dermatomyositis respond to immunotherapeutic agents. New immunomodulatory agents currently being tested in controlled trials may prove promising for difficult cases.

The inflammatory myopathies are a heterogeneous group of subacute, chronic, or acute acquired diseases of skeletal muscle. They have in common the presence of moderate to severe muscle weakness and inflammation in the muscle.1,2 The disorders are clinically important because they are potentially treatable. On the basis of well-defined clinical, demographic, histological, and immunopathological criteria, the inflammatory myopathies form three major and discrete groups: polymyositis, dermatomyositis, and sporadic inclusion-body myositis.1 This review describes current knowledge of the clinical presentation, diagnosis, pathogenesis, and treatment of polymyositis and dermatomyositis. Inclusion-body myositis, a common and important subset as recently reviewed,1,2 is addressed only to outline its distinguishing features in the differential diagnosis of polymyositis.

Epidemiology, genetics, and general clinical features

Dermatomyositis affects both children and adults, and women more than men. Polymyositis is seen after the second decade of life. Inclusion-body myositis is more common in men over the age of 50 than in other population groups.1,3 The frequencies of polymyositis and dermatomyositis as stand-alone disorders or in association with other systemic diseases are unknown. Estimates based on old diagnostic criteria, which cannot distinguish polymyositis from inclusion-body myositis,1,3 range from 0·6 to 1·0 per 100 0001–3 but may not be reliable (see later). In all age-groups, dermatomyositis is the most common and polymyositis the least common; inclusion-body myositis is the commonest myopathy above the age of 50. In children, dermatomyositis is the most frequent inflammatory myopathy but polymyositis is very rare, as recently confirmed.1,3 Genetic factors may have a role, as suggested by rare familial occurrences and association with certain HLA genes, such as DRB1*0301 alleles for polymyositis and inclusion-body myositis,1,3,4 HLA DQA1 *0501 for juvenile dermatomyositis,15 or tumour necrosis factor 308A polymorphism for photosensitivity in dermatomyositis.16 Emerging information on the genetic background of various ethnic groups may allow identification of immune-response genes that predispose certain populations to polymyositis or dermatomyositis.13,17

Both polymyositis and dermatomyositis present with a varying degree of muscle weakness that develops slowly, over weeks to months, but acutely in rare cases.1 Patients report difficulty with everyday tasks, such as rising from a chair, climbing steps, stepping onto a kerb, lifting objects, or combing their hair. Fine motor movements that depend on the strength of distal muscles, such as holding or manipulating objects, are affected late in the course of dermatomyositis and polymyositis, but fairly early in sporadic inclusion-body myositis owing to prominent involvement of distal muscles, especially wrist and finger flexors.1 Early involvement of the quadriceps muscle and ankle dorsiflexors, causing buckling of the knees and frequent falls, is common in sporadic inclusion-body myositis.1 Facial muscles remain normal but mild facial muscle weakness is common in patients with sporadic...
inflammation is seen. Although there may be cases of involvement with perivascular and perimysial taken from such cases, however, subclinical muscle not involve the phalanges. When chronic, the rash contrast to systemic lupus erythematosus, the rash does not involve the phalanges.18 In advanced cases, and in rare acute cases, dysphagia with choking episodes and respiratory muscle weakness occurs. Sensation remains normal. The tendon reflexes are preserved but may be absent in severely weakened or atrophied muscles. Contrary to widespread belief, myalgia is not common, occurring in less than 30% of the patients.

**Specific clinical features**

**Dermatomyositis**

Dermatomyositis is identified by a characteristic rash accompanying or, more commonly, preceding muscle weakness. The skin manifestations include a heliotrope rash (blue-purple discoloration) on the upper eyelids in many cases associated with oedema, and an erythematous rash on the face, neck, and anterior chest (in many patients in a V sign) or back and shoulders (shawl sign), knees, elbows, and malleoli; the rash can be exacerbated after exposure to the sun and is pruritic in some cases. Characteristic is the Gottron rash (figure 1), a raised violaceous rash or papules at the knuckles, prominent in metacarpophalangeal and interphalangeal joints;19 in contrast to systemic lupus erythematosus, the rash does not involve the phalanges. When chronic, the rash becomes scaly with a shiny appearance. Dilated capillary loops at the base of the fingernails with irregular, thickened, and distorted cuticles are also characteristic. The lateral and palmar areas of the fingers may become thickened, and distorted cuticles are also characteristic. A common early abnormality in dermatomyositis resembles the adult disease, except for more frequent extramuscular manifestations (see later). A common early abnormality in children is “misery”, defined as an irritable child who feels uncomfortable, has a red flush on the face, is fatigued, does not socialise, and has a varying degree of proximal muscle weakness.6 A tiptoe gait due to flexion contracture of the ankles is common.1

Dermatomyositis can be associated with cancer1 or may overlap with systemic sclerosis and mixed connective-tissue disease.2,12,21 Fasciitis and thickening of the skin, as seen in chronic dermatomyositis, can also occur in patients with eosinophilia-myalgia syndrome,24 eosinophilic fasciitis, or macrophagic myofasciitis.22

**Polymyositis**

Polymyositis is best defined as a subacute myopathy that evolves over weeks to months, affects adults but rarely children, and presents with weakness of the proximal muscles. Unlike dermatomyositis in which the rash secures early recognition, the actual onset of polymyositis cannot be easily identified.1 Polymyositis mimics many other myopathies and remains a diagnosis of exclusion (panel).26–29 It should be viewed as a syndrome of diverse causes that occurs separately or in association with systemic autoimmune disorders or viral infections in patients who do not have any of the exclusion criteria listed in the panel.

As a stand-alone clinical entity, polymyositis is an uncommon but frequently misdiagnosed disorder. The commonest myopathy misdiagnosed as polymyositis is inclusion-body myositis; this disorder is suspected in retrospect in many cases of presumed polymyositis that have not responded to therapy.1,7 Especially in men older than 50 years, a polymyositis-like disease is inclusion-body myositis until proved otherwise. Other disorders misdiagnosed as polymyositis include toxic and endocrine myopathies, dermatomyositis sine dermatitis, certain dystrophies, and some slowly progressive myopathies commonly starting in late childhood (panel).

**Associated clinical findings (table 1)**

*Extramuscular manifestations*

There are many manifestations outside the muscles. Joint contractures occur mostly in dermatomyositis. Dysphagia is due to involvement of the oropharyngeal striated muscles and upper oesophagus (gastrointestinal ulcerations due to vasculitis and infection were common in children with dermatomyositis before the use of immunosuppressants). Cardiac disturbances include atrioventricular conduction defects, tachyarrhythmias, myocarditis in patients with acute disease,1,2 and heart failure commonly related to hypertension from long-term steroid use. Pulmonary symptoms are due to weakness of the thoracic muscles or interstitial lung disease, which is common in patients with autoantibodies to tRNA inclusion-body myositis.1 The extraocular muscles are never affected, in contrast to myasthenia in which they are affected early.1 The neck extensor muscles may be involved, causing difficulty in holding up the head (head drop). In advanced cases, and in rare acute cases, dysphagia with choking episodes and respiratory muscle weakness occurs. Sensation remains normal. The tendon reflexes are preserved but may be absent in severely weakened or atrophied muscles. Contrary to widespread belief, myalgia is not common, occurring in less than 30% of the patients.
synthetases or a mucin-like glycoprotein (KL-6). Subcutaneous calcifications (figure 1), occur only in dermatomyositis, in some cases extruding on the skin and causing ulcerations, infections, and pain, especially at sites of compression (elbows, buttocks, back). General symptoms include fever, malaise, weight loss, arthralgia, and Raynaud’s phenomenon when polymyositis or dermatomyositis is associated with another connective-tissue disease.

Malignant disorders
Although all the inflammatory myopathies can have a chance association with malignant disease, especially in older age-groups, the frequency of cancer is definitely increasing in dermatomyositis. A slightly increased frequency reported in polymyositis must be confirmed with use of updated diagnostic criteria. The most common cancers are those of the ovaries, gastrointestinal tract, lung, and breast and non-Hodgkin lymphomas. Continuous vigilance is required for early recognition, especially in older people and during the first 3 years after disease onset. In patients without risk factors, expensive, radiological blind searches for occult malignant disease are not practical or fruitful. A complete annual physical examination with pelvic, breast (mammogram, if indicated), rectal (with colonoscopy, according to age and family history) radiographs and a chest film should suffice. A report that blind search with abdominal–pelvic and thoracic CT scans increased the yield by 28% needs confirmation. In Asian patients, among whom nasopharyngeal cancer is more common, careful assessment of ears, nose, and throat is suggested.

Overlap syndrome
Polyomyositis and dermatomyositis are seen in association with various autoimmune and connective tissue diseases (table 1). The term overlap syndrome is used loosely to indicate that certain clinical signs are shared by both disorders. Accordingly, it is only dermatomyositis, and not polymyositis, that truly overlaps and only with various autoimmune and connective tissue diseases. The term overlap syndrome is used loosely to indicate that certain clinical signs are shared by both disorders. Accordingly, it is only dermatomyositis, and not polymyositis, that truly overlaps and only with connective-tissue disease. Certain signs seen in these two disorders, such as sclerotic thickening of the dermis, contractures, oesophageal hypomotility, microangiopathy, and calcium deposits, are also present in dermatomyositis but not polymyositis; by contrast, signs of rheumatoid arthritis, lupus, or Sjögren’s syndrome are rare in dermatomyositis and mixed connective-tissue disease. Certain signs seen in these two disorders, such as sclerotic thickening of the dermis, contractures, oesophageal hypomotility, microangiopathy, and calcium deposits, are also present in dermatomyositis but not polymyositis; by contrast, signs of rheumatoid arthritis, lupus, or Sjögren’s syndrome are rare in dermatomyositis (table 1). A report that dermatomyositis can overlap with lupus needs confirmation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dermatomyositis</th>
<th>Polymyositis</th>
<th>Inclusion-body myositis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at onset</strong></td>
<td>All ages</td>
<td>&gt;18 years</td>
<td>&gt;50 years</td>
</tr>
<tr>
<td>Familial association</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Extramuscular features</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Associated disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connective-tissue disease*</td>
<td>Only with scleroderma and mixed connective-tissue disease</td>
<td>Yes, with all</td>
<td>Yes, in up to 20% of cases</td>
</tr>
<tr>
<td>Overlap syndrome†</td>
<td>Only with scleroderma and mixed connective-tissue disease</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Systemic autoimmunity disease</td>
<td>Rarely</td>
<td>Frequently</td>
<td>Infrequently</td>
</tr>
<tr>
<td>Malignant disorders</td>
<td>Yes, in up to 15% of cases</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Viruses</td>
<td>Unproven</td>
<td>Yes‡</td>
<td>Yes‡</td>
</tr>
<tr>
<td>Parasites and bacteria</td>
<td>No</td>
<td>Yes§</td>
<td>Yes§</td>
</tr>
<tr>
<td>Drug-induced myotoxicity</td>
<td>Rarely</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*In patients with Sjögren’s disease or rheumatoid arthritis.
†Overlap denotes that certain signs are common to both disorders; by contrast, “association” denotes that two disorders can coexist. H€V and HTLV-1. | Includes parasitic (protozoa, cestodes, and nematodes), tropical, and bacterial myositis (pyomyositis). | Drugs include penicillamine (for dermatomyositis and polymyositis), zidovudine (for polymyositis), contaminated tryptophan (for a dermatomyositis-like illness), and lipid-lowering drugs rarely. Other myotoxic drugs can cause myopathy but not inflammatory myopathy.

Table 1: Conditions and factors associated with inflammatory myopathies

Clinical characteristics of polymyositis

**Myopathic weakness**
Evolves over weeks to months, spares facial and eye muscles, and presents as difficulty in climbing steps, rising from a chair, lifting objects, combing hair.

**Disease onset**
Above the age of 18 years

**Features the patient **DOES NOT** have**
Rash (characteristic of dermatomyositis)
Family history of neuromuscular diseases
Exposure to myotoxic drugs, especially penicillamine, zidovudine, and rarely statins
Endocrine disease (hypothyroidism, hyperthyroidism, hyperparathyroidism, hypercortisolism)
Neurogenic disease (excluded by electromyography and neurological examination)
Dystrophies and metabolic myopathies (excluded by history and muscle biopsy)
Inclusion-body myositis (excluded by clinical examination and muscle biopsy)

**Possible associations**
Other autoimmune or viral infections, such as: lupus, rheumatoid arthritis, Sjögren’s syndrome, Crohn’s disease, vasculitis, sarcoidosis, primary biliary cirrhosis, adult coeliac disease, chronic graft-versus-host disease, discoid lupus, ankylosing spondylitis, Behçet’s syndrome, myasthenia gravis, acne fulminans, dermatitis herpetiformis, psoriasis, Hashimoto’s disease, granulomatous diseases, agammaglobulinaemia, hyperesoinophilic syndrome, Lyme disease, Kawasaki disease, autoimmune thryomocytopenia, hypergamaglobulinaemia purpura, hereditary complement deficiency, HIV and HTLV-1 infection.

Reconsider polymyositis
If the diagnosis was based on Bohan and Peter’s criteria, in patients with:

**Disease onset before the age of 18**
Slow-onset myopathy that evolved over months to years (in such cases think of inclusion-body myositis or dystrophy)

Fatigue and myalgia, without muscle weakness, even if a transient rise in creatine kinase activity is seen (such patients may have fibromyalgia or fasciitis, and their muscle biopsy sample is normal or shows very few inflammatory cells in the endomysial septae)

No typical histological features of polymyositis
Diagnosis
The clinical diagnosis of polymyositis and dermatomyositis is confirmed by three laboratory examinations: serum muscle enzyme concentrations, electromyography, and muscle biopsy. In certain cases of dermatomyositis, skin biopsy can be helpful.

The most sensitive muscle enzyme assay is creatine kinase, which is increased up to 50 times in active disease. Aspartate and alanine aminotransferases, lactate dehydrogenase, and aldolase are also increased. Although creatine kinase concentration usually parallels disease activity, it can be normal in some patients with active dermatomyositis; in the active phases of polymyositis, the creatine kinase concentration is always increased.

Needle electromyography shows increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. The voluntary motor units consist of low-amplitude polyphasic units of short duration. Although not disease specific, these findings are useful to confirm active myopathy. Presence of spontaneous activity can help to distinguish active disease from steroid-induced myopathy, except if the two coexist.

The muscle biopsy is the most crucial test for establishing the diagnosis, but also the most common cause of misdiagnosis due to erroneous interpretation. In dermatomyositis, the inflammation is predominantly perivascular or in the interfascicular septae and around rather than within the fascicles. The intramuscular blood vessels show endothelial hyperplasia with tubuloreticular profiles, fibrin thrombi, especially in children, and obliteration of capillaries resulting in reduction of capillary density (figure 2). The muscle fibres undergo phagocytosis and necrosis, commonly in groups (microinfarcts) involving a portion of a muscle fasciculus, or the periphery of the fascicle, resulting in perifascicular atrophy. This atrophy, characterised by two to ten layers of atrophic fibres at the periphery of the fascicles, is diagnostic of dermatomyositis, even in the absence of inflammation (figure 2). The skin lesions show perivascular inflammation with CD4-positive cells in the dermis; in chronic stages there is dilatation of superficial capillaries. Skin histopathology distinguishes dermatomyositis from other papulosquamous disorders but not from cutaneous lupus.

In polymyositis, multifocal lymphocytic infiltrates surround and invade healthy muscle fibres (figure 2). The inflammation is primary, a term used to indicate that lymphocytes (CD8-positive cells) invade histologically healthy muscle fibres expressing MHC class I antigens. We refer to this lesion as the CD8/MHC-I complex (see later). In chronic stages, connective tissue is increased and may react with alkaline phosphatase. When, in
addition to primary inflammation, there are vacuolated muscle fibres with basophilic granular deposits around the edges (rimmed vacuoles) and congophilic amyloid deposits within or next to the vacuoles, the diagnosis of inclusion-body myositis is likely.\textsuperscript{1,3–5,56} Errors in the histological diagnosis of polymyositis can be avoided by three steps. First, primary inflammation should be demonstrated. This step has become an essential criterion because it distinguishes polymyositis from toxic, infectious (parasitic, bacterial [pyomyositis]), granulomatous, metastasising, and sarcolemmal or enzymatic proteins that exclude specific targets. MHC-I antigens are markers of aggressive disease and they do occur in patients with interstitial lung disease (table 3).\textsuperscript{3,4,6} A report that antibodies to signal-recognition particle, anti-Jo-1, accounts for 80% of all the autoantibodies and their specificity in the pathogenesis of polymyositis and dermatomyositis remains unclear because they are not specific for tissue or disease subset, they occur in less than 25% of patients, and they do occur in patients with interstitial lung disease without myositis.\textsuperscript{3,4,6} A report that antibodies to signal-recognition particles are markers of aggressive disease with cardiomyopathy and poor response to therapies has not been confirmed.\textsuperscript{4} Other autoantibodies include anti-Mi-2, anti-polymyositis-Scl, found in dermatomyositis with scleroderma, and anti-KL6 associated with interstitial lung disease (table 3).

\section*{Immunopathogenesis}

The autoimmune origin of polymyositis and dermatomyositis is supported by their association with other autoimmune disorders, autoantibodies, and histocompatibility genes; the evidence of T-cell-mediated myocytotoxicity or complement-mediated microangiopathy; the possible maternal microchimerism in juvenile forms; and their response to immunotherapies. However, no specific target antigens have been identified, and the agents initiating self-sensitisation remain unknown.

\section*{Autoantibodies}

Autoantibodies against nuclear or cytoplasmic antigens, directed against ribonucleoproteins involved in protein synthesis (anti-synthetase) or translational transport (anti-signal-recognition particle), are found in about 20% of patients (table 3).\textsuperscript{3,4} These antibodies are useful clinical markers because of their frequent association with interstitial lung disease. The antibody against histidyl-tRNA synthetase, anti-Jo-1, accounts for 80% of all the anti-synthetases and seems to confer specificity for identifying a disease subset that combines myositis, non-erosive arthritis, and Raynaud’s phenomenon. The importance of these antibodies and their specificity in the pathogenesis of polymyositis and dermatomyositis remains unclear because they are not specific for tissue or disease subset, they occur in less than 25% of patients, and they do occur in patients with interstitial lung disease without myositis.\textsuperscript{3,4,6} A report that antibodies to signal-recognition particles are markers of aggressive disease with cardiomyopathy and poor response to therapies has not been confirmed.\textsuperscript{4} Other autoantibodies include anti-Mi-2, anti-polymyositis-Scl, found in dermatomyositis with scleroderma, and anti-KL6 associated with interstitial lung disease (table 3).
Immunopathology of dermatomyositis

The primary antigenic target in dermatomyositis is the endothelium of the endomysial capillaries (figure 3). The disease begins when putative antibodies directed against endothelial cells activate complement C3. Activated C3 leads to formation of C3b, C3bNEO, and C4b fragments and C5b–9 membranolytic attack complex (MAC), the lytic component of the complement pathway.49,66,67 MAC, C3b, and C4b are detected early in the patients’ serum 68 and are deposited on capillaries before inflammatory or structural changes are seen in the muscle.49,66,67 Sequentially, the complement deposits induce swollen endothelial cells, vacuolisation, capillary necrosis, perivascular inflammation, ischaemia, and destruction of muscle fibres.1,2,46,53 The characteristic perifascicular atrophy (figures 2 and 3) reflects endofascicular hypoperfusion, which is prominent distally. Finally, there is striking reduction in the number of capillaries per muscle fibre with compensatory dilatation of the lumen of the remaining capillaries.46,53 Cytokines and chemokines69–72 related to complement activation are released; they upregulate vascular-cell adhesion molecule (VCAM-1) and intercellular adhesion molecule (ICAM-1) on the endothelial cells and facilitate the egress of activated T cells to the perimysial and endomysial spaces (figure 3). T cells and macrophages through their integrins (very late activation antigen 4 and leucocyte-function-associated antigen 1) bind to the adhesion molecules and pass into the muscle through the endothelial cell wall. The predominant lymphocytes are B cells and CD4-positive T cells, consistent with a humorally mediated process.1,2,49–53,73 Gene expression profiling in muscles of genetically susceptible children showed interferon inducible genes implying virus-driven autoimmune dysregulation.74 However, no viruses have been amplified.

Immunopathology of polymyositis

In polymyositis and inclusion-body myositis, CD8-positive cells invade MHC-I-antigen expressing muscle fibres.50–53

Cytotoxic T cells

T-cell lines established from muscle biopsy material are cytotoxic to autologous myotubes.75 In vivo, the CD8-positive cells send spike-like processes into non-necrotic muscle fibres, traverse the basal lamina, and focally invade the muscle cell.73 The autoinvasive cells express the memory and activation markers CD45RO and ICAM-176

Autoantibodies associated with myositis

<table>
<thead>
<tr>
<th>Autoantibodies associated with myositis*</th>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-aminoacyl-tRNA synthetases (in 20% of patients)</td>
<td>tRNA* synthetase†‡</td>
</tr>
<tr>
<td>Anti-Jo-1†</td>
<td>tRNAhis synthetase</td>
</tr>
<tr>
<td>Anti-PL-7</td>
<td>tRNA* synthetase</td>
</tr>
<tr>
<td>Anti-PL-12</td>
<td>tRNA* synthetase</td>
</tr>
<tr>
<td>Anti-EJ</td>
<td>tRNA* synthetase</td>
</tr>
<tr>
<td>Anti-OJ</td>
<td>tRNA* synthetase</td>
</tr>
<tr>
<td>Anti-KS</td>
<td>tRNA* synthetase</td>
</tr>
<tr>
<td>Anti-signal recognition particle</td>
<td>SRP-complex</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Anti-Mi-2 (10–15% of dermatomyositis and polymyositis)</td>
<td>Nuclear helicase</td>
</tr>
<tr>
<td>Anti-polyomysitis-Scl (15% of dermatomyositis with scleroderma)</td>
<td>Nuclear complex</td>
</tr>
<tr>
<td>Anti-KL6 (in patients with interstitial lung disease)</td>
<td>Mucin-like glycoprotein (on alveoli or bronchial epithelial cells)</td>
</tr>
</tbody>
</table>

SRP=signal recognition particle. *The antibodies are found mostly in polymyositis and dermatomyositis, and occasionally in inclusion-body myositis, when the myositis is associated with another connective-tissue disorder. †Some Jo-1-positive patients with polymyositis or dermatomyositis have the triad of non-erosive arthritis, interstitial lung disease, and Raynaud’s phenomenon; 50% of them have interstitial lung disease. ‡7% of these patients also have antibodies against the cognate tRNAhis.

Table 3: Various autoantibodies associated with polymyositis, dermatomyositis, and some cases of inclusion-body myositis

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and contain perforin and granzyme granules that are directed towards the surface of the fibres. Thus, the perforin pathway seems to be the major cytotoxic effector mechanism. By contrast, the Fas-Fas-L-dependent apoptotic process is not functionally involved, despite expression of Fas antigen on muscle fibres and Fas-L on the autoinvasive CD8-positive cells. The coexpression of the anti-apoptotic molecules BCL2, FLICE (Fas-associated death domain-like interleukin-1-converting enzyme inhibitory protein [FLIP]), and human IAP-like protein (hILP), may confer resistance of muscle to Fas-mediated apoptosis (figure 4).

In polymyositis and inclusion-body myositis but not dermatomyositis, certain CD8-positive cells of specific T-cell-receptor (TCR) families are clonally expanded both in the circulation and in muscle. In individual patients, the CDR3 region, the antigen-binding region of the TCR of the autoinvasive CD8-positive cells, has conserved aminoacid sequences, which suggest that T-cell expansion is driven by a common antigen, possibly an autoantigen. Remarkably, only the autoinvasive (autoaggressive) T cells are clonally expanded; the non-invasive bystander T cells are clonally diverse.

In one case, a single clone of γδ T cells of a single clone were the primary cytotoxic effectors. When the γδ TCR of these cells was transfected into a TCR-deficient mouse hybridoma cell line, the transfectants could be stimulated with an unknown autoantigen on human myoblasts. This is the first indication that in γδ T-cell mediated polymyositis the autoaggressive T cells recognise muscle antigens.

**MHC expression**
Muscle fibres do not normally express MHC class I or II antigens. In polymyositis and inclusion-body myositis, however, widespread overexpression of MHC class I, and occasionally MHC II, is seen even in areas remote from the inflammation. In human myotubes, MHC molecules are upregulated by interferon-γ. Although in transgenic mice MHC-I expression was proposed to act as an inciting event triggering polymyositis with myositis-specific antibodies, the observed histopathology was not typical of myositis. Furthermore, in human polymyositis upregulation of MHC-I alone does not trigger T-cell activation or endomysial infiltration. Another MHC molecule, the non-polymorphic non-classic HLA G, is upregulated in vitro by interferon-γ and is expressed on muscle fibres of patients with polymyositis (and inclusion-body myositis). Because HLA G protects human muscle cells from immune-cell-mediated lysis in vitro, it could also partially protect muscle fibres in vivo.

**Costimulatory molecules**
If the autoinvasive CD8-positive cells are driven by specific antigens, as the clonally expanded TCR gene rearrangements indicate, the MHC-I molecule on the muscle fibres should be able to present antigenic peptides to the TCR. For primary T-cell antigenic stimulation a second signal is required and provided by the B7 family of costimulatory molecules. Muscle fibres do not express the classic costimulatory molecules B7-1 (CD80) or B7-2 (CD86); instead, they express a functional B7-related molecule defined by the monoclonal antibody BB-1. Indeed, the MHC-I/BB1-positive muscle fibres make direct cell-to-cell contact with their CD28 or CTLA-4 ligands on the autoinvasive CD8-positive cells (figure 4). The B7-related costimulatory molecule LICOS (ligand of inducible costimulator) and the costimulatory molecule CD40 are also upregulated on muscle fibres.
Cytokines, cytokine signalling, chemokines, and metalloproteinases

In the muscles of patients with polymyositis or dermatomyositis, there is overexpression of the signal transduction and activation of transducers type I, indicating cytokine upregulation. Various cytokines and their mRNA, including interleukins 1, 2, 6, and 10, tumour necrosis factor α, interferon γ, and transforming growth factor β, are amplified in polymyositis and dermatomyositis. Some of them, such as interferon γ and interleukin 1b, may have a myocytotoxic effect whereas others, such as transforming growth factor β, may promote chronic inflammation and fibrosis. Muscle-fibre necrosis occurs via the perforin granules released by the autoaggressive T cells. Death of the muscle fibre is mediated by a form of necrosis rather than apoptosis, presumably because of the counterbalancing effect or protection by the antiapoptotic molecules BCL2, hILP, and FLIP which are upregulated in polymyositis and inclusion-body myositis. Fas is also expressed, but it does not mediate apoptosis in the muscle. The upregulated NCAM on degenerating muscle fibres may enhance regeneration. After successful immunotherapy, there is downregulation of cytokines with reduction of inflammation and fibrosis. Chemokines, a class of small cytokines, including interleukin 8 (CXCL8), RANTES (CCL5), MCP-1 (CCL2), Mig CXCL9), and IP-10 (CXCL10) are also overexpressed in the endomysial inflammatory cells, the extracellular matrix, and the muscle fibres; they may facilitate trafficking of activated T cells to the muscle or promote tissue fibrosis. The matrix metalloproteinases MMP-2 and MMP-9, which promote the migration of lymphocytes through extracellular matrix, are also overexpressed on the muscle fibres and the autoinvasive CD8-positive cells.

Viral infections

Although several viruses (coxsackieviruses, influenza, parvoviruses, paramyxoviruses, cytomegalovirus, Epstein-Barr virus) and bacteria (Borrelia burgdorferi, streptococci) have been inversely associated with chronic and acute myositis, sensitive PCR studies have not amplified viral genome from muscle of these patients. A proposed molecular mimicry based on structural homology between coxsackieviruses and Jo-1 synthethase has not been proved. The best evidence of a viral connection is with retroviruses. At least six different retroviruses have been associated with polymyositis and inclusion-body myositis. Monkeys infected with simian immunodeficiency virus and human beings infected with HIV and HTLV-1 develop polymyositis either as an isolated clinical entity or concurrently with other manifestations of AIDS or HTLV-1 infection. HIV seroconversion may coincide with myoglobinuria and acute myalgia, suggesting that myotropism for HIV can be symptomatic early in the infection. The retroviruses are found only in occasional endomysial macrophages and do not replicate within the muscle fibres or cause persistent infection. In HIV-1 and HTLV-1 polymyositis, CD8-positive, non-viral-specific, cytotoxic T cells invade MHCI-antigen-expressing non-necrotic muscle fibres in a pattern identical to retrovirus-negative polymyositis. Virus-induced cytokines, secreted also in situ by the virus-infected macrophages, could trigger T-cell activation and MHCI upregulation. The relationship between systemic retroviral infection and local autoimmune processes in muscle is not precisely understood. In principle, there are two possibilities: either the autoimmune attack is triggered by mimicry between retroviral and muscle antigens, or the autoimmune process is non-specifically induced via bystander stimulation.

Treatment

The goals of therapy are to improve the ability to carry out activities of daily living by increasing muscle strength and to ameliorate extramuscular manifestations (rash, dysphagia, dyspnoea, arthralgia, fever). There have been very few controlled clinical trials, most on dermatomyositis and inclusion-body myositis. Overall, dermatomyositis responds better than polymyositis, and inclusion-body myositis is difficult to treat. Although when the strength improves, the serum creatine kinase concentration falls concurrently, the reverse is not always true because treatments (eg, plasmapheresis) can lower the serum creatine kinase concentration without improving strength. This effect has been misinterpreted as "chemical improvement", and has formed the basis for the common habit of "chasing" or "treating" the creatine kinase concentration instead of the muscle weakness. The following agents are used in the treatment of polymyositis and dermatomyositis.

Corticosteroids

Prednisone is the first-line drug, but its application remains empirical. We start with 80–100 mg per day for 3–4 weeks, and taper the dose over 10 weeks to alternate-day administration. Although most patients respond to some degree and for some time, others become steroid resistant and the addition of an immunosuppressive drug becomes necessary. The decision to initiate such therapy is based on the need for a steroid-sparing effect, when despite steroid responsiveness the patients develop complications; the inability to lower the high steroid dose without precipitating a relapse; inefficacy of a 2–3-month course of high-dose prednisone; and rapidly progressive weakness and respiratory failure.

Immunosuppressive drugs

Selection of an immunosuppressive drug remains empirical and depends on personal experience and the relative efficacy/safety ratio. Azathioprine (orally, 2.5–3.0 mg/kg) takes 4–6 months to work. A controlled trial in 1980 showed benefit of azathioprine. Methylprednisolone (orally, up to 25 mg weekly) acts more quickly than azathioprine. A rare side-effect is pneumonitis, which may be difficult to distinguish from the interstitial lung disease associated with Jo-1 antibodies. Cyclosporin (orally, 100–150 mg twice daily) may also benefit childhood dermatomyositis. Mycophenolate mofetil (2 g per day) is emerging as a promising and well tolerated drug. Cyclophosphamide (0.5–1.0 g/m²) intravenously has shown mixed results; it may help patients with interstitial lung disease, but the evidence remains circumstantial.

Other treatments

Plasmapheresis was not found to be helpful in a double-blind, placebo-controlled study. Total lymphoid irradiation has helped in a few patients but its long-term side-effects curtail its use. Intravenous immunoglobulin (2 g/kg) in uncontrolled series was promising. In the first double-blind study conducted for dermatomyositis, intravenous immunoglobulin was effective not only in improving muscle strength but also in resolving the underlying immunopathology, as shown by repeated muscle biopsies. The improvement can be impressive; it begins after the first infusion but is short lived in most patients.
primary inflammation (CD8-positive/MHC-I complex) is normal strength do not have polymyositis. Seventh, if exclude myogenic origin of increased "liver enzymes" patients presenting with fatigue and increased activities of muscle tested with needle electromyography should not myopathies (dystrophies, toxic, metabolic). Fourth, endomysial inflammation also occurs in non-immune inclusion-body myositis is more common. Third, available, polymyositis is rare in neuromuscular clinics; is rare. Although no accurate epidemiological data are polymyositis as a stand-alone entity is excluded, taking into account that the criteria of Bohan is rare.154–156 In a small cohort, at least a third of patients are left with mild to severe disability.154,155 Older age and association with cancer are factors associated with poor prognosis. Pulmonary fibrosis, frequent aspiration pneumonias due to oesophageal dysfunction, and calcinosis in dermatomyositis are associated with increased morbidity.155,156 In small cohorts, the 5-year survival was 95% and the 10-year survival 84%.156

Prognosis

Although the disease outcome has substantially improved, Proportion to 70% of patients. Our approach

The following sequential, step-by-step, empirical escalating approach has been successful in our patients. Step 1 is prednisone. Step 2 is azathioprine or méthotrexate (methotrexate acts faster but no comparative trials are available); the choice depends on personal experience. In aggressive cases, steps 1 and 2 may be combined from the outset. Step 3 is intravenous immunoglobulin (this may be used as step 2). Step 4 is cyclosporin, mycophenolate mofetil, chlorambucil, or cyclophosphamide, used individually or in various combinations with steps 1–3, as dictated by disease severity, coexisting disorders, or the patient’s age. Superiority of a specific combination remains unproven.150

Future immunotherapies

Although antigen-specific therapies are not in the offing, some rational therapeutic approaches are currently being investigated with agents that: block signal transduction in T lymphocytes (such as FK506, rapamycin, CAMPATH, or monoclonal antibodies against costimulatory molecules CD28/CTLA-4); are directed against cytokines, such as monoclonal antibodies against tumour necrosis factor α, soluble receptors to tumour necrosis factor α and β interferons; and interfering with integrins and their receptors.154–158

Conclusion

On the basis of our own experience and that of others in major neuromuscular centres, the diagnosis and treatment of dermatomyositis and polymyositis could be improved by modification of many common practices. First, all disorders that mimic polymyositis should be excluded, taking into account that the criteria of Bohan and Peter cannot separate polymyositis from inclusion-body myositis or other toxic, necrotising, and dystrophic myopathies. Second, polymyositis as a stand-alone entity is rare. Although no accurate epidemiological data are available, polymyositis is rare in neuromuscular clinics; inclusion-body myositis is more common. Third, endomysial inflammation also occurs in non-immune myopathies (dystrophies, toxic, metabolic). Fourth, muscle tested with needle electromyography should not be sampled by biopsy until a month later. Fifth, in patients presenting with fatigue and increased activities of serum aminotransferases or lactate dehydrogenase, the creatine kinase concentration should be also checked to exclude myogenic origin of increased “liver enzymes” and avoid misdirection towards liver disease and liver biopsy. Sixth, patients with active polymyositis have muscle weakness; patients presenting with myalgias but normal strength do not have polymyositis. Seventh, if primary inflammation (CD8-positive/MHC-I complex) is not demonstrable, the diagnosis of polymyositis is doubtful. Eighth, the goal of therapy is to improve strength; creatine kinase is a good indicator of disease activity but not the target of therapy. Ninth, when therapies for presumed polymyositis have lowered the creatine kinase concentration but not improved strength, the patient should be reassessed, the muscle biopsy sample re-examined, and a second biopsy considered to exclude inclusion-body myositis or dystrophy. Finally, when the patient’s strength has improved but is not fully restored, maintenance therapy with immunosuppressive drugs or alternate-day prednisone should be continued.

Conflict of interest statement

None declared.

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