

The inflammatory myopathies

JULIEN P. DE JAGER MB BCH, FRACGP, FRACP

The inflammatory myopathies – polymyositis, dermatomyositis, inclusion body myositis and immune-mediated necrotising myopathy – are rare but in many cases, treatable causes of muscle weakness.

MedicineToday 2013; 14(9): 67-71

The inflammatory myopathies are a group of rare conditions that usually present in general practice as a patient with muscle weakness and/or an elevated serum creatine kinase (CK) level. Possible extramuscular manifestations include skin rashes, fever and weight loss. Recently there have been important advances in our understanding of these conditions and in their management.¹ The group includes polymyositis, dermatomyositis, inclusion body myositis and immune-mediated necrotising myopathy (also known as necrotising autoimmune myopathy and a potential drug side effect). These conditions are differentiated on the basis of their pattern of presentation, patient age at onset and immunohistopathologic features. Their classification is summarised in the box on this page.²

Although these conditions are rare, it is important they be considered in the differential diagnosis of muscle weakness as treatments are available for polymyositis and dermatomyositis,

and untreated they can lead to significant muscle wasting, disability and even death. In addition, it is important to recognise immune-mediated necrotising myopathy as it can be a side effect of drug therapy, especially with statins or proton pump inhibitors.

The inflammatory myopathies should be distinguished from 'overlap myositis', where muscle is involved in another connective tissue disorder.³ In addition, the inflammatory myopathies are not usually considered in patients with muscle pain but no weakness, where the differential diagnosis includes conditions such as fibromyalgia and polymyalgia rheumatica.

DIAGNOSIS

History taking should cover patient age, onset and distribution of weakness, accompanying extramuscular features (particularly a skin rash), exposure to drugs and chemicals, infection with viruses (especially HIV), bacteria or other organisms, unusual habits that might cause myopathy (such as excessive tea drinking) and family history. Infections can cause focal myositis that is potentially painful.³ Both hypothyroidism and hyperthyroidism can give rise to myopathies with elevated CK levels.

CLASSIFICATION OF THE INFLAMMATORY MYOPATHIES

The 1975 classification system of Bohan and Peter remains widely used:

- A. Polymyositis
- B. Dermatomyositis
 - (i) Adult, with or without malignancy
 - (ii) Juvenile or childhood
- C. Myositis with other connective tissue disease
- D. Inclusion body myositis
- E. Drug- or infection-related myositis*

Based on Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; 292: 344-347.

* To which should be added immune-mediated necrotising myopathy.

Professor de Jager is Senior Visiting Rheumatologist, Gold Coast Hospital, Southport; and Professor of Medicine, Griffith University, Brisbane, Qld.

SERIES EDITORS: Dr Jane Zochling, MB BS, FRACP, MMed (ClinEpi), PhD, is a Research Fellow at the Menzies Research Institute, University of Tasmania, Hobart, Tas. Professor Lyn March, MB BS, MSc, PhD, FRACP, FAFPHM, is Professor of Medicine at The University of Sydney, Department of Rheumatology at Royal North Shore Hospital, Sydney, NSW.



Australian
Rheumatology
Association

MEDICAL RESEARCH COUNCIL (MRC) SCALE FOR MUSCLE STRENGTH

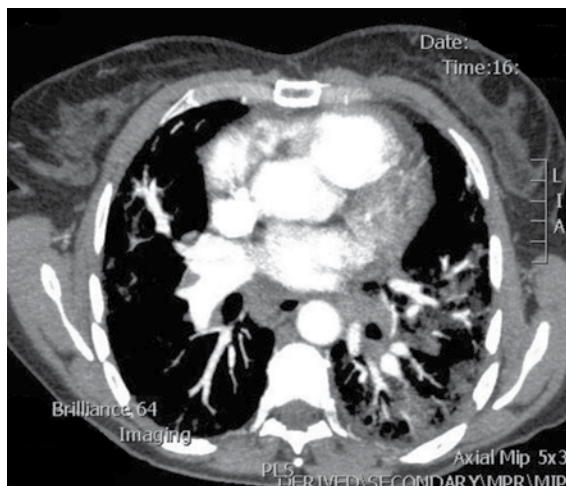
- 0 = No contraction
- 1 = Contracts, no movement
- 2 = Full range of movement with gravity eliminated
- 3 = Full range of movement in presence of gravity
- 4 = Full range of movement against some resistance
- 5 = Normal power

Physical examination should include a systematic evaluation of muscle strength and function, along with joint and neurological evaluation. A standard scoring system for muscle strength is useful (see the box on this page). Pain is uncommon in the inflammatory myopathies, but inflamed muscle may be tender. Cardiac muscle may be involved.

In addition to raised CK levels, investigations often show increased levels of lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). This may cause confusion with a liver disorder.

Recent reports of patients incorrectly diagnosed with polymyositis illustrate its clinical similarity to a variety of other disorders.⁴ For example, two Tasmanian patients with myopathy caused by nematode infection were initially misdiagnosed with polymyositis.⁵ Similarly, a five-year follow up of 268 patients diagnosed with polymyositis or dermatomyositis in the Netherlands found that almost 40% had been diagnosed in the interim with a different condition, including sporadic inclusion body myositis, rhabdomyolysis and muscular dystrophies.⁶ Immune-mediated necrotising myopathy, which can be triggered by viral infections, cancer and drugs such as statins, is also now more likely to be encountered than polymyositis, dermatomyositis or sporadic inclusion body myositis. Viral myositis is usually self-limiting.

Figure 1. Lung CT in a patient with a 20-year history of anti-Jo-1-positive polymyositis, arthritis and interstitial lung disease. The lungs show acute inflammatory changes as well as established honeycombing, especially in the base of the left lung.



SPECIALIST REFERRAL

Diagnosis and investigation of patients with suspected inflammatory myopathy is complex, and their management requires special expertise to achieve good outcomes and minimise the adverse effects of treatment. It is therefore advisable to refer patients for specialist diagnostic workup and shared management.

POLYMYOSITIS

Polymyositis has probably been over-diagnosed in the past, but our improved understanding of its pathogenesis and the development of more sophisticated testing techniques have shown it to be the rarest of the four disorders discussed here.^{4,6} Polymyositis has an incidence of two to nine cases per million population per year. Possible triggers include picornaviruses, such as coxsackie virus.

In polymyositis, there is proximal muscle weakness. Respiratory and cardiac muscle may be involved, and swallowing may be affected. Raynaud's phenomenon, rash, arthritis and pulmonary fibrosis may occur (particularly when the specific antibody anti-Jo-1 is present – see below). Serum CK level is usually elevated, often in proportion to muscle damage, along with levels of LDH, AST and ALT.⁵ Electromyography shows abnormalities such as myopathic potentials, abnormal spontaneous activity and fibrillation potentials.

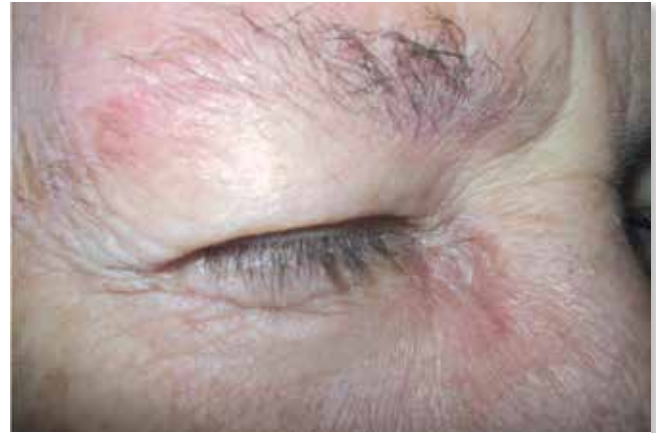
Muscle biopsy shows muscle fibre necrosis and infiltration with variable regeneration. Vasculitis is rarely seen. A distinguishing feature is the presence of endomysial infiltrates of CD8+ T cells and macrophages invading non-necrotic muscle fibres that express MHC-1 antigen.⁴ More recently, a correlation has been seen between type 1 interferon gene expression in peripheral blood and disease activity, which is even more pronounced in dermatomyositis than in polymyositis.^{7,8}

Two classes of autoantibodies are found in polymyositis:⁹

- tissue-specific antibodies directed against muscle – antimyosin and antimyoglobin antibodies occur in more than 80% of patients with polymyositis (note that these antibodies are not routinely measured)
- nonspecific autoantibodies directed against ubiquitous nuclear and cytoplasmic constituents.

Antinuclear antibody is positive in 25 to 70% of people with polymyositis. Of the extractable nuclear antigen (ENA) antibodies, anti-Ro (SS-A) is present in 10 to 15% of people with polymyositis, anti-La (SS-B) in 5 to 20%, antipolymyositis-scleroderma (Pm-Scl) in 8% and anti-Mi-2 in less than 5% of cases, suggesting the myopathy may be secondary to a connective tissue disease.

Myositis-associated anticytoplasmic antibodies have considerable importance



Figures 2a and b. Rash in patients with dermatomyositis. a (left). Gottron's papules and rash in a child with juvenile dermatomyositis, showing rough red areas over the nail beds and knuckle pads. b (right). Localised heliotropic rash, which was proven on biopsy to be dermatomyositis, in a patient with muscle weakness and raised serum creatine kinase levels. The patient was subsequently found to have a gastrointestinal stromal tumour.

as they may define subgroups of patients with specific extramuscular organ involvement and consequent poorer long-term prognosis. These antibodies are directed against aminoacyl-transfer RNA synthetases. In polymyositis, the target autoantigen is histidyl tRNA synthetase (known commonly as Jo-1). Anti-Jo-1 antibodies are present in about 15 to 25% of all patients with polymyositis, often those with concurrent interstitial lung disease, mechanic's hand, arthritis, rash and Raynaud's phenomenon (Figure 1).

MRI with T1-weighting, T2-weighting and sequences using fat suppression techniques (short tau inversion recovery) can be very useful both in showing the site and extent of muscle involvement and in differentiating myositis from oedema, fibrosis and calcification. It is also useful in patchy disease to identify potential muscle biopsy sites and to monitor disease for improvement (or help in defining relapse when weakness presents later in treatment). It may replace muscle biopsy in children with juvenile myositis.

DERMATOMYOSITIS

Dermatomyositis is similar to polymyositis, distinguished clinically only by its characteristic skin changes. These include a rash on the knuckle pads (Gottron's sign),

elbows, shoulders, neck, knees or thighs, and facial changes such as 'heliotrope rash' of the eyelids with periorbital oedema (Figures 2a and b). Other features of dermatomyositis include proximal muscle weakness and electromyography changes, CK elevation and an MRI appearance indistinguishable from polymyositis.

However, dermatomyositis differs from polymyositis histopathologically. In polymyositis, the cellular infiltrate is mainly within the fibre or fascicle, and abnormal fibres are scattered throughout the fascicle. In dermatomyositis, there is a perifascicular infiltrate, the primary lesion being located in blood vessels. The mononuclear cell infiltrate comprises mainly B cells, CD4+ T cells and plasmacytoid dendritic cells. Abnormal muscle fibres are grouped in one portion of the fascicle. In the past, this damage was attributed to ischaemia, as vasculitis is common in dermatomyositis. However, the injury to muscle in dermatomyositis has now been shown to resemble the injury to skin.⁸ Although there is endothelial damage in the vessels, there is perifascicular atrophy with cytokine type 1 interferon and tumour necrosis factor alpha damage to capillaries and myofibres.

Malignancy may be present in 25% of adults aged over 45 years with

dermatomyositis, as opposed to 10 to 15% of those with polymyositis. Malignancy is unlikely to be present in younger adults with dermatomyositis and is not associated with juvenile dermatomyositis or juvenile polymyositis.

In juvenile dermatomyositis, calcinosis may be prominent. It may precede the other features of the disorder, possibly as a result of vasculitis.

Evolving guidelines for diagnosing juvenile dermatomyositis have resulted in increased use of muscle MRI, allowing invasive electromyography and muscle biopsies to be avoided in many children. The myositis-specific antibody anti-Mi-2 is seen in 5% of children with dermatomyositis, often in association with Gottron's sign, the V-shawl sign (macular erythema on the posterior neck and shoulders), heliotrope rash of the eyelids and cuticle overgrowth.

INCLUSION BODY MYOSITIS

Sporadic inclusion body myositis usually occurs after the age of 50 years, with a male to female ratio of three to one. The clinical findings including both proximal and distal muscle involvement with wasting and weakness, which can become striking. Histopathological features suggest an ageing-based degenerative pathogenic

THE INFLAMMATORY MYOPATHIES: PRACTICE POINTS

- The inflammatory myopathies are rare but beware a missed diagnosis as it can lead to significant muscle wasting and debility.
- Patient care is usually shared between the specialist rheumatologist and GP.
- Treatment usually involves a high-dose corticosteroid initially; more than half the patients may require an immunosuppressant.
- Patients should be encouraged to undertake active rehabilitation once disease activity is controlled.
- Avoid, prevent and monitor for corticosteroid side effects, as patients often need high doses for prolonged periods.
- Be proactive in cardiovascular disease prevention as this is the major cause of mortality.
- Be mindful of infections in the immunosuppressed patient. Ensure the patient is adequately vaccinated against pneumococcus and influenza, and monitor for herpes zoster.

cascade. Light microscopy of muscle biopsy specimens may show rimmed vacuoles in muscle fibres and a lymphocytic infiltrate, and electron microscopy may reveal accumulation of beta-amyloid and tau protein in muscle. Inclusion body myositis is poorly understood but is possibly an RNA sequestration disease (in which the accumulation of noncoding RNA causes toxicity, as postulated to occur in neurodegenerative conditions such as Alzheimer's disease).¹⁰

Muscle biopsy specimens from patients with sporadic inclusion body myositis have an inflammatory component, at least in the early stage, but this responds poorly to immunosuppression, unlike polymyositis and dermatomyositis. Occasionally there is an initial response, which may confuse the diagnosis. The usual outcome is a slow progressive loss of function.

Diseases with pathological features that strongly resemble those of sporadic inclusion body myositis but lack evidence of lymphocytic inflammation are assumed to be hereditary inclusion body myositis. Hereditary inclusion body myositis includes several autosomal recessive and autosomal dominant syndromes of progressive muscle weakness, which have specific clinical presentations.

IMMUNE-MEDIATED NECROTISING MYOPATHY

Most researchers now consider immune-mediated necrotising myopathy to be an entity distinct from polymyositis and dermatomyositis. However, myonecrosis can also occur in severe polymyositis and dermatomyositis, and recovery is possible. Immune-mediated necrotising myopathy may follow infections, exposure to drugs such as statins or proton pump inhibitors or to chemicals, and is also seen in heat stroke. The histological feature is extensive necrotic muscle with relatively sparse infiltrates (usually macrophages and T cells) and often extremely high serum CK levels. Recovery may be slow.

In statin myopathy, levels of antibodies to HMGCoA-reductase have been found to correlate with severity of disease and CK levels. These antibodies may also be found in patients with nonstatin-related immune-mediated necrotising myopathy. A test for these antibodies is available in Western Australia but at the time of writing is still under research.¹¹

MANAGEMENT

The management of polymyositis and dermatomyositis is similar. After a diagnosis of either of these conditions is clearly established (clinical features, CK

measurement, electromyography, muscle biopsy and/or MRI in children with suspected juvenile dermatomyositis) then drug treatment to suppress inflammation should begin as soon as possible.⁷ Patients are usually investigated and begin treatment in hospital under specialist care. Follow-up care is then shared between the GP and consultant physician. Patients often require a prolonged period of rehabilitation, which usually begins in hospital.

Inclusion body myositis may show some initial response to immunosuppressive treatment, but when response ceases these drugs are mostly withdrawn. Rehabilitation and the provision of aids to help patients manage at home as long as possible are the main interventions.

Immune-mediated necrotising myopathy is treated by withdrawal of the offending agent (if known), immunosuppression when there is evidence of an inflammatory process and supportive treatment.

Medication***Prednisolone***

Prednisolone 0.5 to 1 mg/kg per day in a single daily dose is given initially to treat polymyositis, dermatomyositis and in certain circumstances, inclusion body myositis and immune-mediated necrotising myopathy. Pulse methylprednisolone 1 g daily for three days may be used for induction if there is very severe muscle weakness and rash. The daily prednisolone dose is then tapered: at first by 10 mg every two to four weeks until a dose of 30 mg daily is reached; then by 5 mg every two weeks to a dose of 20 mg daily; followed by 2.5 mg every two weeks to a dose of 10 mg daily; and finally by 1 mg each month.¹² CK level and clinical assessment are usually the guide to decreasing prednisolone therapy over six to eight months.

Measures to prevent osteoporosis should be instituted at the beginning of treatment, but hypercalcaemia should be avoided because of the possibility of calcinosis.

Immunosuppressants

Around half of patients with polymyositis or dermatomyositis may need additional therapy because of adverse effects of prednisolone, such as corticosteroid myopathy, or failure to respond adequately to prednisolone. No trials have shown the superiority of one immunosuppressant over another. Options include:

- methotrexate 10 to 15 mg per week in a single weekly dose given orally or intramuscularly, increasing to up to 30 to 50 mg per week in a single dose; folic acid supplements are given away from the weekly dose
- azathioprine 2 to 3 mg/kg daily, split into two doses; serum thiopurine methyltransferase levels should be checked before azathioprine treatment to identify patients at risk of potentially fatal myelosuppression from the usual dose – if enzyme levels are low, a lower dose or alternative therapy should be used
- mycophenolate mofetil, starting with 500 mg twice daily and increasing to 1000 mg twice daily
- cyclophosphamide given orally or intravenously as pulse doses
- intravenous rituximab or cyclosporin; these may be used in some specialist clinics
- human immunoglobulin infusions; evidence for their efficacy comes from case reports and some small controlled trials.¹³ Human immunoglobulin is usually used after first-line agents have failed – it is obtained by application to the relevant State Blood Bank.

Hydroxychloroquine

In dermatomyositis, skin rashes are often treated with hydroxychloroquine.

Nondrug treatment

Extensive aerobic activity should be avoided until the CK level has normalised. However, active rehabilitation and physiotherapy are vital from early in the illness to prevent contractures and later to improve muscle function. Rehabilitation

and physiotherapy may need to be intensive in the recovery phase and should be part of an overall rehabilitation plan.

In patients who are immunosuppressed, it is important to be mindful of infections and to ensure they are adequately vaccinated against pneumococcus and influenza. They should also be monitored for herpes zoster.

Measures to reduce the risk of cardiovascular disease are also important as this is the major cause of mortality in patients with polymyositis or dermatomyositis.

PROGNOSIS

Prognosis of the inflammatory myopathies has improved greatly since they were first recognised because of early diagnosis, aggressive management and improved immunosuppressant drugs. A recent follow up of patients with polymyositis or dermatomyositis in South Australia showed a favourable outcome in 18 to 90%, with an average 60% survival at five years.¹⁴ The

standardised mortality ratio was 1.75 – i.e. the risk of mortality was increased 75% compared with the age- and sex-matched population. In those who died, the cause of death was cardiovascular disease in one-third, infection in 22% (especially pneumonia) and malignancy in 10%.

In inclusion body myositis, there is usually a slow decline over many years. In immune-mediated necrotising myopathy, recovery is variable, depending on the original insult to muscle, treatment and support; some patients recover fully. However, there are no good data regarding this condition.¹⁵

CONCLUSION

In patients with an inflammatory myopathy, the shared task of the GP and rheumatologist is to try to suppress organ inflammation, while also intervening to prevent the complications of the disease and its treatment. Practice points for GPs are summarised in the box on page 70. **MT**

REFERENCES

1. Emste F, Reed A. Idiopathic inflammatory myopathies: current trends in pathogenesis, clinical features and up-to-date treatment recommendations. *Mayo Clin Proc* 2013; 88: 83-105.
2. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; 292: 344-347.
3. Lazarou IN, Guerne PA. Classification, diagnosis, and management of idiopathic inflammatory myopathies. *J Rheumatol* 2013; 40: 550-564.
4. Amato AA, Griggs RC. Unicorns, dragons, polymyositis, and other mythological beasts. *Neurology* 2003; 61: 288-289.
5. Dennett X, Siejka SJ, Andrews JR, Beveridge I, Spratt DM. Polymyositis caused by a new genus of nematode. *Med J Aust* 1998; 168: 226-227.
6. Bronner IM. Long term outcome in polymyositis and dermatomyositis. *Ann Rheum Dis* 2006; 65: 1456-1461.
7. Walsh RJ, Kong SW, Yao Y, et al. Type 1 interferon-inducible gene expression in blood is present and reflects disease activity in dermatomyositis and polymyositis. *Arthritis Rheum* 2007; 56: 3784-3792.
8. Greenberg SA, Fiorentino D. Similar topology of injury to keratinocytes and myofibres in dermatomyositis skin and muscle. *Br J Dermatology* 2009; 160: 464-465.
9. Lazarou IN, Guerne PA. Classification, diagnosis and management of idiopathic inflammatory myopathies. *J Rheumatol* 2013; 40: 550-564.
10. Greenberg SA. Inclusion body myositis: review of recent literature. *Curr Neurol Neurosci Rep* 2009; 9: 83-89.
11. Werner JL, Christopher-Stine L, Ghazarian SR, et al. Antibody levels correlate with creatine kinase levels and strength in anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. *Arthritis Rheum* 2012; 64: 4087-4093.
12. Tymms K, Webb J. Dermatopolymyositis and other connective tissue diseases. *J Rheumatol* 1985; 12: 1140-1148.
13. Dalakos MC, Dalakas MC, Illa I, et al. A controlled trial of high dose intravenous immunoglobulin infusion for treatment of dermatomyositis. *N Engl J Med* 1993; 329: 1993-2000.
14. Lemaye V, Hakendorf P, Woodman RJ, et al. Mortality and its predominant causes in a large cohort of patients with biopsy-determined inflammatory myositis. *Intern Med J* 2012; 42: 191-197.
15. Liang C, Needham M. Necrotising autoimmune myopathy. *Curr Opin Rheumatol* 2011; 23: 612-619.

COMPETING INTERESTS: Professor de Jager participates in the OPAL (Optimising Patient Outcomes in Australian Rheumatology) Group, which receives support from Roche, and a research study sponsored by UCB.