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CORE TRAINING FOR DOCTORS



**Edited by Dr Daniel JB Marks,** Academic Clinical Fellow in Translational Medicine, and **Dr Philip J Smith,** Academic Clinical Fellow and Specialist Registrar in Gastroenterology, University College London

# Dermatomyositis

Dermatomyositis is an idiopathic acute inflammatory disorder, characterized by inflammation of skeletal muscle, progressive symmetrical proximal myopathy and classical cutaneous manifestations. It affects both children and adults, and women more frequently than men. Dermatomyositis is the commonest inflammatory myopathy in all age groups, with an estimated prevalence of 0.6–1.0 per 100 000 (Dalakas and Hohlfeld, 2003). Its association with malignancy mandates a thorough search for underlying neoplasia in all cases.

In 1975, Bohan and Peter proposed five subsets of myositis:

1. Dermatomyositis
2. Polymyositis
3. Myositis with cancer
4. Childhood dermatomyositis
5. An overlap syndrome with other collagen vascular disorders (Bohan and Peter, 1975).

A further two subtypes have subsequently been recognized: amyopathic dermatomyositis and inclusion body myositis (Euwer and Sontheimer, 1991; Sayers et al, 1992).

This review describes the clinical approach to patients with dermatomyositis that will guide a focused history and examination, as well as the modes of their investigation and management.

## Clinical features

Bohan and Peter proposed a set of five criteria to help in the diagnosis of dermatomyositis and polymyositis:

1. Progressive, proximal symmetrical weakness
2. Elevated levels of muscle enzymes
3. Abnormal electromyography
4. Abnormal muscle biopsy
5. Cutaneous disease (dermatomyositis only).

**Dr Satveer Mahil** *is ST3 in Dermatology,* **Dr Daniel Marks** *is Academic Clinical Fellow in Translational Medicine,* **Dr Mary McCormack** *is Consultant Oncologist and* **Professor Anisur Rahman** *is Professor of Rheumatology, University College London, London WC1E 6JJ*

*Correspondence to: Dr S Mahil (satveer.mahil@gmail.com)*

Definite dermatomyositis requires the presence of four of these including rash, whereas probable dermatomyositis requires three. In addition, visceral and joint involvement are well recognized.

### Skeletal muscle disease

The symmetrical proximal myopathy in dermatomyositis is slowly progressive over weeks to months. It manifests with myalgia, fatigue and weakness. The patient has difficulty climbing stairs, rising from squatting or sitting, lifting objects, raising arms to brush hair, and elevating the head and neck when supine. In contrast to lower motor neuron disorders, there are no fasciculations and tendon reflexes are typically preserved. Tenderness of affected muscles on palpation may be present but is often variable. Facial and extraocular muscles are classically spared. If muscle strength is normal but the patient manifests cutaneous disease, the patient may have amyopathic dermatomyositis.

### Cutaneous disease

The course of the cutaneous lesions does not necessarily parallel that of muscle involvement: it may precede development of myopathy and persist after myositis has resolved. The pathognomonic heliotrope rash is a symmetrical, violaceous discolouration of the periorbital skin, often with associated oedema (*Figure 1a*). There may be scaling, desquamation and dilated veins over the eyelids. Scalp involvement manifests as non-scarring alopecia or a violaceous psoriasiform dermatitis.

There may be an erythematous, possibly photoaggravated, poikilodermatous rash on the face, neck, anterior chest and upper back ('shawl sign', *Figure 1b*), and upper-lateral thighs ('holster sign'). Poikiloderma refers to the combination of atrophy, dyspigmentation and telangiectasia. Other characteristic cutaneous features include malar erythema and violaceous erythema on the extensor surfaces. Rarely vesicobullous lesions, erosions and exfoliative erythroderma may develop.

Gottron's papules are also pathognomonic (*Figure 1c*): these are violaceous papules and plaques overlying the metacarpophalangeal and interphalangeal

joints, which may feature scale and telangiectasia. Capillary microscopy of the nailfolds will highlight characteristic periungual telangiectasia and irregular cuticular hypertrophy with small haemorrhagic infarcts. The patient may have 'mechanic's hands', with rough cracked lateral and palmar aspects of the fingers as a result of hyperkeratosis.

The cutaneous features of dermatomyositis may be exacerbated by certain drugs, so a comprehensive medication review is mandated. Common culprits include non-steroidal anti-inflammatory drugs, hydroxyurea and penicillamine.

### Oesophageal disease

Dysphagia is present in 15–50% of patients with inflammatory myopathy, and carries poor prognosis, with increased risk of aspiration pneumonia and malnutrition (Callen and Wortmann, 2006). Proximal dysphagia is steroid-responsive and caused by involvement of the striated muscle of the oropharynx and proximal oesophagus (Ebert, 2009). Distal dysphagia relates to disease of non-striated muscle and may manifest in patients with overlap collagen vascular disorders such as systemic sclerosis.

### Pulmonary disease

Respiratory involvement is more common in patients with oesophageal disease and is similarly associated with poor prognosis; incidence is 5–45% (Fathi and Lundberg, 2005). Manifestations include interstitial lung disease, ventilatory failure as a result of weakness of the intercostal muscles, or aspiration secondary to dysphagia. Pulmonary fibrosis and opportunistic infections may arise as complications of drug treatment.

### Cardiac disease

Although rarely symptomatic, cardiac involvement may be evident in up to 50% of patients (Lundberg, 2006). Subclinical cardiac anomalies are predominantly conduction delays and arrhythmias found incidentally on electrocardiography. Cardiac disease may also manifest as heart failure, coronary artery disease, myocarditis, pericarditis and valvular disease. Hypertension may result from long-term steroid or ciclosporin use.

### Other systemic features

Arthralgia and arthritis may be present. The latter is classically non-erosive, symmetrical and affects the small joints of the hands, wrists and ankles. Contractures may occur. General constitutional symptoms may also include fever, malaise, weight loss and Raynaud's phenomenon, as well as features of overlap with systemic sclerosis or mixed connective tissue disease.

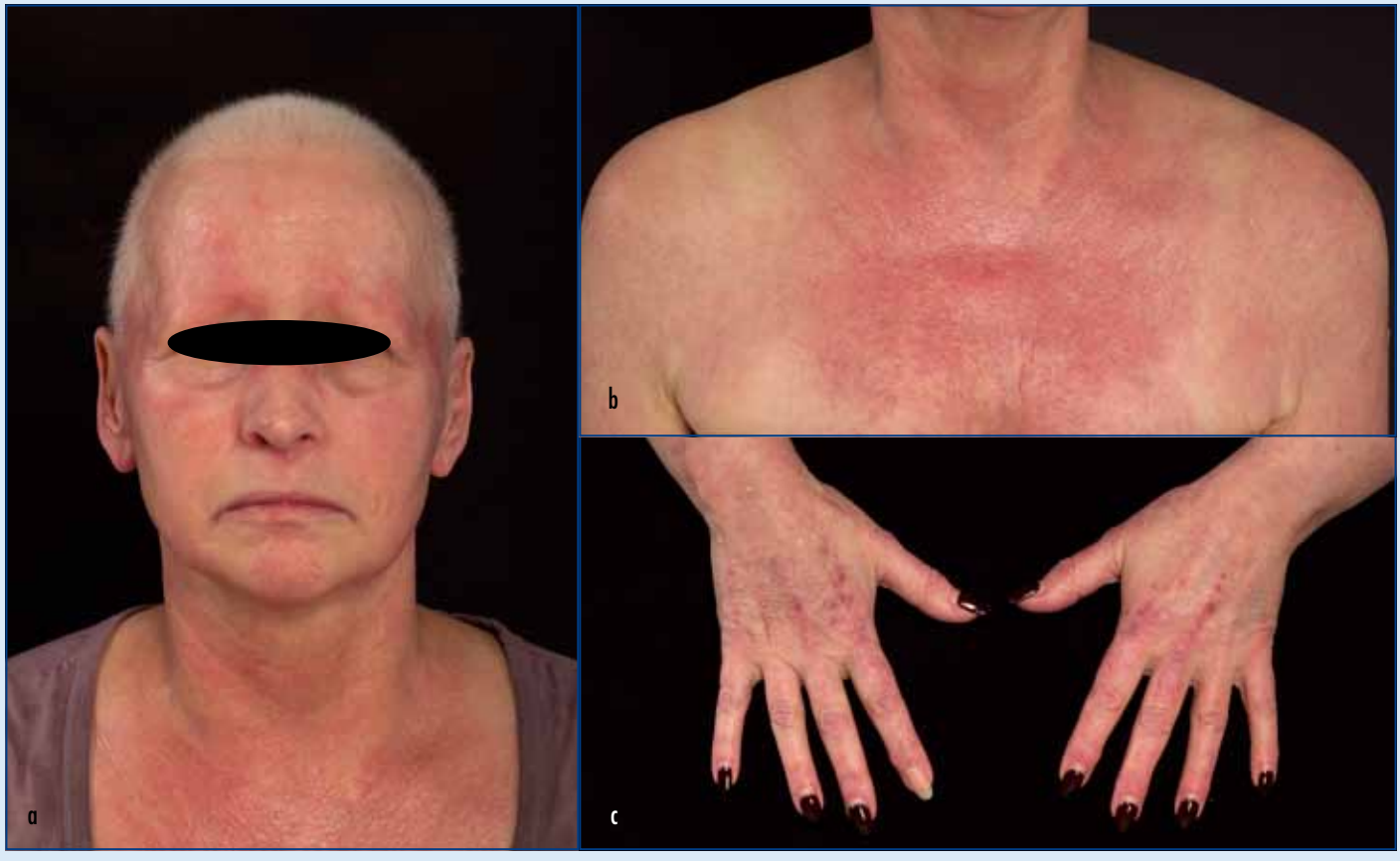
## Association with malignancy

Dermatomyositis is associated with increased risk of malignancy (*Table 1*), in which it arises as a paraneoplastic phenomenon

**Table 1. Cancers most strongly associated with dermatomyositis**

| |
|---|
| Ovarian carcinoma |
| Bronchial carcinoma |
| Colorectal carcinoma |
| Pancreatic carcinoma |
| Non-Hodgkin's lymphoma |
| Nasopharyngeal carcinoma (south-east Asian patients only) |

*Figure 1. Characteristic dermatological findings. a. Heliotrope rash, (b) shawl sign, and (c) Gottron's papules.*



(Siguregeirsson et al, 1992). There are wide variations in reported frequencies of underlying malignancy, ranging from 6–60%, possibly as a result of variable definitions of myositis in different studies (Callen and Wortmann, 2006). There is some evidence of ethnic variation, with south-east Asian patients having increased rates of nasopharyngeal carcinoma (Peng et al, 1995).

Neoplasia has been classically linked to older patients (aged over 50 years). More recent reports also suggest increased risk in younger patients (Hill et al, 2001; Sparsa et al, 2002), although in juvenile disease there is more commonly an antecedent upper respiratory tract or gastrointestinal infection (Feldman et al, 2008). Malignancy may be recognized before, concurrent with or after onset, but most cancers are diagnosed within 3 years of the identification of myositis. Dermatomyositis also predicts high mortality (Andras et al, 2008).

The course of dermatomyositis often parallels that of the malignancy, improving after treatment and recurring during relapse (Osako et al, 2007). Predictors of underlying neoplastic disease include absence of antinuclear antibodies and of myositis-specific autoantibodies, rapid onset, normal serum creatinine kinase concentration on presentation, and clinical or histological evidence of cutaneous vasculitis (Fudman and Schnitzer, 1986; Hunger et al, 2001; Sparsa et al, 2002).

## Investigations

### Blood tests

Active disease is associated with raised serum creatinine kinase concentrations, which may be up to 50 times the upper limit of normal. Lactate dehydrogenase, alanine aminotransferase and aldolase levels may be similarly elevated. While creatinine kinase and lactate dehydrogenase may be useful for monitoring response to treatment, a caveat is that their levels can be normal in active disease and do not correlate with prognosis.

Antinuclear antibodies (homogeneous fluorescence pattern) are often positive in patients with dermatomyositis, as are a number of myositis-specific and myositis-associated antibodies (*Table 2*) (Love et al, 1991). Anti-aminoacyl-transfer RNA synthetase antibodies are a group of myositis-specific autoantibodies that bind to a family of enzymes that catalyze the ATP-dependent attachment of a particular amino acid to its transfer RNA during protein synthesis; anti-Jo1 (anti-histidyl tRNA synthetase) is the most common (*Table 2*) (Gunawardena et al, 2009). They are associated with a severe clinical phenotype called the anti-synthetase syndrome, characterized by myositis, interstitial lung disease, arthritis, Raynaud's phenomenon and mechanic's hands.

Anti-Mi2 is a myositis-specific autoantibody that is directed against a nuclear ATPase autoantigen, present in 25–30% of patients. It is specific but not sensitive, and associated with the hallmark cutaneous manifestations of dermatomyositis. Its presence carries better overall prognosis, with milder muscle disease and heightened response to steroid therapy (Gunawardena et al, 2009). Autoantibodies to the signal recognition particle ribonucleoprotein complex are found in fewer than 3% of patients, and appear to be associated with severe, refractory disease and poor prognosis (Targoff et al, 1990).

### Electromyography

Classic electromyography findings in active myopathy are increased spontaneous activity with fibrillations, complex repetitive discharges and positive sharp waves. Electromyography can be used to identify affected muscles and hence target biopsy.

### Magnetic resonance imaging

Magnetic resonance imaging is a useful non-invasive investigation for early diagnosis of myositis, assessment of the extent of inflammation, guidance of muscle biopsy and monitoring response to treatment (*Figure 2*). It is sensitive for detecting muscle oedema (Garcia, 2000), which appears hyper-intense on T2-weighted images. Signal in subcutaneous adipose tissue is also seen in dermatomyositis. Fatty infiltration is indicative of chronic muscular inflammation that may be less responsive to therapy.

### Muscle biopsy

The muscle selected for biopsy should be guided by electromyography and/or magnetic resonance imaging to enhance diagnostic yield. Dermatomyositis is considered to be a microvasculopathy, arising as a result of complement-mediated injury against the intramuscular vasculature, which leads to muscle ischaemia and inflammation. As such, immunohistochemistry classically shows membrane attack complexes (C5b–9) deposited in endomysial capillaries and there is subsequent reduced intramuscular capillary density and endothelial hyperplasia with fibrin thrombi (Emslie-Smith and Engel, 1990). Inflammatory infiltrates are perivascular or in the interfascicular septae (Dalakas, 2002). There is degeneration of groups of muscle fibres within a muscle fasciculus. If those at the periphery of the fasciculus are involved, classical perifascicular atrophy results.

Polymyositis, by contrast, is thought to be a muscle-specific antigen-mediated disorder, with muscle necrosis resulting from

**Table 2. Myositis-specific and myositis-associated autoantibodies**

| Autoantibody | | | Clinical features |
|---|---|---|---|
| Myositis-specific | Anti-synthetase antibodies | Anti-Jo1 (anti-histidyl tRNA synthetase)<br>Anti-PL7 (anti-threonyl)<br>Anti-PL12 (anti-alanyl)<br>Anti-OJ (anti-isoleucyl)<br>Anti-EJ (anti-glycyl)<br>Anti-KS (anti-asparaginyl)<br>Anti-Ha (anti-tyrosyl)<br>Anti-Zo (anti-phenylalanine) | Anti-synthetase syndrome: myositis, interstitial lung disease, arthritis, mechanic's hands, Raynaud's phenomenon |
| | Anti-Mi2 | | Cutaneous involvement, good prognosis |
| | Anti-SRP | | Severe refractory disease, poor prognosis |
| Myositis-associated | Anti-polymyositis-Scl | | Associated with overlap syndromes with features of systemic sclerosis and myositis |
| | Anti-U1-RNP | | Associated with overlap syndromes with features of systemic sclerosis, myositis and systemic lupus erythematosus |

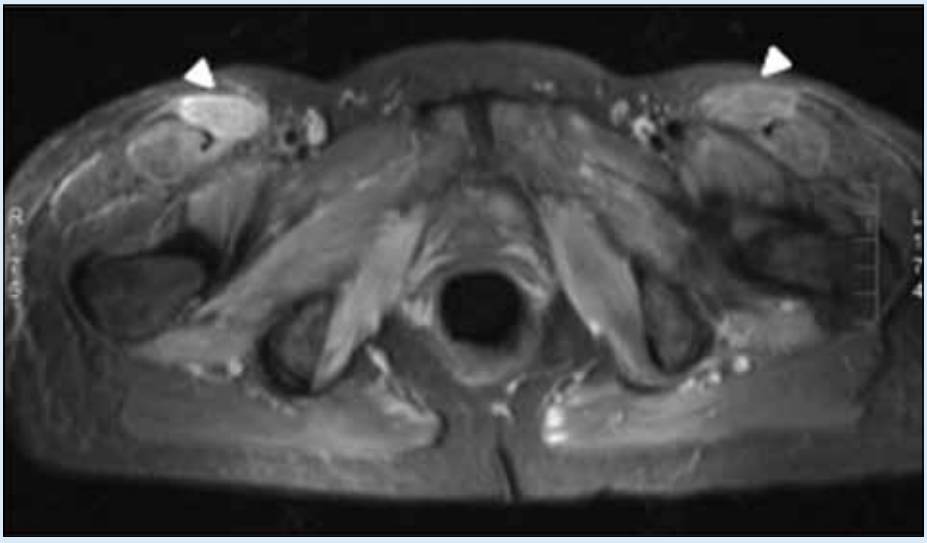


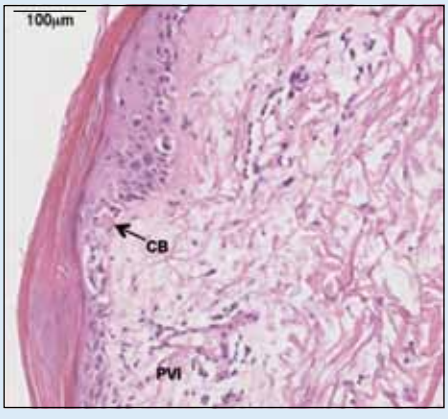
*Figure 2. T1 inverse recovery magnetic resonance imaging demonstrating diffuse high signal consistent with active inflammation in multiple muscle groups bilaterally including the sartorius muscles (arrowheads), internal and external obturators, and adductors.*

cytotoxic T cells targeting muscle fibres that express MHC class I antigens. Muscle biopsy shows intrafascicular inflammatory infiltrates with scattered single muscle fibre necrosis, and immunohistochemistry reveals upregulation of MHC class I expression on the sarcolemma.

### Skin biopsy

Skin biopsy may reveal interface dermatitis with perivascular lymphocytic inflammation (*Figure 3*). This may be difficult to distinguish from cutaneous lupus erythematosus without additional immunofluorescence studies, which are typically negative in dermatomyositis (although may be falsely positive in photo-damaged skin) (Callen and Wortmann, 2006).

*Figure 3. Skin biopsy reveals interface dermatitis with basal vacuolar change, perivascular lymphocytic infiltration (PVI) and an occasional Civatte body (CB).*




### Respiratory, cardiac and oesophageal disease

Chest radiography, pulmonary function tests (including diffusion capacity) and possibly high resolution computed tomography should be performed to assess for pulmonary complications of dermatomyositis (Fathi and Lundberg, 2005). Daily forced vital capacity measurements should take place in inpatients with suspected respiratory muscle weakness. Electrocardiography and echocardiography may detect cardiac involvement (Lundberg, 2006). Bedside swallow assessment should be conducted to highlight any potential risk of aspiration; more formal dynamic imaging or oesophageal manometry may be required for full evaluation (Ebert, 2009).

### Search for malignancy

All patients should be investigated for malignancy to aid early diagnosis and reduce mortality. A thorough history, examination, routine blood testing and chest radiography must be performed in all patients. Subsequent investigations should be selected according to the patient demographic and clinical presentation, but may include mammography, computed tomography scanning of chest, abdomen and pelvis, faecal occult blood testing and gastrointestinal endoscopy, and ear, nose and throat assessment (Hill et al, 2001; Callen, 2002; Sparsa et al, 2002). If negative, this assessment should be repeated regularly, for example annually for the first 3 years following diagnosis. The role of fluorodeoxyglucose-positron emission tomography (FDG-PET) combined with computed tomography is still under evaluation.

## Management

There have been few randomized controlled trials to inform physicians about optimal therapy, and consequently this is mostly based on clinical experience (Choy and Isenberg, 2002). The main aims are to improve muscle strength and achieve clinical stabilization or remission. The patient should be managed within a multidisciplinary team consisting of rheumatologists and dermatologists, with regular input from physiotherapy, occupational therapy, speech and language therapy and dieticians. Oncology input should be sought where appropriate: tumour-associated dermatomyositis is typically more refractory than idiopathic disease, and successful treatment of the underlying malignancy often improves the clinical course (Hill et al, 2001).

Standard first-line therapy for dermatomyositis is prednisolone. Starting doses of 1 mg/kg (40–80 mg)/day are typical for 1–2 months until clinical response, followed by a slow tapering regimen over 10 weeks to a maintenance dose of 5–10 mg/day (Cordeiro and Isenberg, 2006; Dalakas, 2010). Patients presenting acutely unwell with severe features, or those not responding to oral immunosuppression, may require pulsed methylprednisolone (1 g daily for 3 days) to achieve rapid remission, although there is no randomized controlled trial evidence for this. Bone protection should be addressed to reduce disability associated with long-term steroid use (Choy and Isenberg, 2002).

Approximately 25% of patients do not respond to steroids, and 20–25% develop significant steroid-related side-effects (Callen, 2000). The addition of a further immunosuppressive drug may be required for recalcitrant disease or as a long-term steroid-sparing agent. Azathioprine and methotrexate are widely used and well tolerated, with methotrexate possibly having more rapid onset of therapeutic response. Ciclosporin, tacrolimus or mycophenolate mofetil are alternatives. Intravenous immunoglobulin may be used in refractory cases, with short-lived improvements in both the

myositis and cutaneous disease (Dalakas et al, 1993). It is usually well tolerated but expensive and requires repeated infusions every 6–8 weeks. Cyclophosphamide administered intravenously monthly for 3–6 months may be favoured in patients with associated vasculitis, respiratory or bulbar involvement. Monoclonal target antibodies are now emerging as novel agents for dermatomyositis, with case reports of successful treatment with anti-tumour necrosis factor (TNF) antagonist agents (infliximab) (Hengstman et al, 2003) and B cell depletion (rituximab) (Levine, 2005).

Cutaneous disease may not respond to the immunosuppressants used to treat myositis. Owing to the photosensitivity, daily use of a broad-spectrum sun block is recommended. Topical steroids or tacrolimus (0.1% twice daily), and oral hydroxychloroquine (200–400 mg daily) may be effective and well tolerated.

Treatment regimens should be tailored to the individual patient. At least one-third are left with residual disability. Therapeutic response and disease relapse can be monitored by measuring serial serum muscle enzyme concentrations, muscle oedema on serial magnetic resonance imaging scans, repeated clinical assessment of muscle power (such as 'manual muscle testing') and extra-skeletal muscle involvement, and patient questionnaires about physical function and quality of life. Although the assessment of several domains is recommended, fully validated disease activity and myositis damage indices have not yet been established (Cordeiro and Isenberg, 2006).

## Conclusions

Dermatomyositis is an idiopathic myopathy with characteristic cutaneous findings. Clinicians should be vigilant for its potential visceral manifestations and the association with underlying malignancy. Therapy uses immunosuppressive agents, and it is optimally managed in a multidisciplinary environment. BJHM

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## KEY POINTS

- Dermatomyositis is characterized by progressive symmetrical proximal myopathy and classic cutaneous manifestations.
- The course of the cutaneous disease may not parallel that of the muscle disease.
- Oesophageal and pulmonary involvement carry poor prognosis.
- Diagnosis requires a combination of assessment of clinical features, serum muscle enzyme levels, myositis-specific autoantibodies, magnetic resonance imaging, electromyography and muscle biopsy.
- Although serum creatinine kinase and lactate dehydrogenase may be used to monitor response to treatment, levels may be normal in active disease.
- Dermatomyositis is associated with increased risk of malignancy; most cancers are diagnosed within 3 years of the diagnosis of myositis.
- First-line therapy is steroid but 25% of patients do not respond.
- Alternate immunosuppressants include azathioprine, methotrexate and cyclophosphamide. Intravenous immunoglobulin, tumour necrosis factor antagonists and rituximab are emerging as effective therapies.
- Cutaneous disease may require topical steroid, tacrolimus or oral hydroxychloroquine.

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