



Idiopathic inflammatory myopathies - a guide to subtypes, diagnostic approach and treatment

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The Idiopathic Inflammatory Myopathies – a guide to subtypes, diagnostic approach and treatment

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Abstract –

The idiopathic inflammatory myopathies are a group of conditions characterised by inflammation of muscles (myositis) and other body systems. The diagnosis can be challenging due to the many potential clinical features and extra-muscular manifestations, which may be seemingly unrelated. An accurate diagnosis requires up to date understanding of the clinical manifestations, different clinical subtypes and appropriate interpretation of investigations including newly described serological subtypes.

This review will detail the approach to the diagnosis of an idiopathic inflammatory myopathy, based on up to date knowledge. The recently updated classification criteria and treatment options will also be described.

Keywords

Idiopathic inflammatory myopathies

Myositis

Dermatomyositis

Polymyositis

Inclusion body myositis

Introduction

The idiopathic inflammatory myopathies (IIMs) are a group of autoimmune conditions characterised by inflammation of muscle (myositis) and other organ systems, resulting in widespread organ dysfunction, increased morbidity and early mortality. Knowledge of the clinical manifestations of the IIMs and our ability to treat them have dramatically progressed since publication of the Bohan and Peter criteria in 1975[1,2]. This review aims to outline the clinical features of the IIMs, current classification criteria, the association of autoantibodies to clinical features and current recommended treatment.

Epidemiology

The IIMs are relatively rare conditions with an overall reported incidence of 11/million person-years (10 for men and 13 for women) and a prevalence of 14/100,000[3].

The peak age range of IIM onset is 45-60 years for adults and 5-15 years for children. Apart from inclusion body myositis (IBM), all IIM subtypes occur more commonly in women (ratio 2:1); IBM occurs twice as commonly in men as women[4].

Subtypes

Traditionally, the IIMs have been divided into subtypes according to their clinical features. Recent advances have identified that more clinically distinct subtypes exist than were originally recognised.

Dermatomyositis and Polymyositis

Dermatomyositis (DM) and polymyositis (PM) are both characterised by myositis (muscle inflammation) and systemic involvement[5][6]. Myositis usually involves the proximal musculature of the limbs leading to weakness and fatigue, especially on tasks such as standing from a seated position or reaching up for highly placed objects.

The systemic manifestations (i.e. involvement of organs other than skeletal muscle) are important aspects of each disease. Possible systemic features include dysphagia[7], dysphonia, interstitial lung disease (ILD)[8], subcutaneous calcification[9], dilated cardiomyopathy, arrhythmias, atrioventricular defects and constitutional features, such as fatigue, fever and weight loss. DM is particularly associated with an increased risk of cancer development (see section entitled "cancer-associated myositis").

DM can be distinguished from PM by its typical cutaneous features, which include Gottron's papules (Figure 1), Gottron's sign, heliotrope rash (Figure 2), V-sign rash, mechanics' hands (Figure 3), shawl sign rash and erythroderma[10]. Gottron's papules are red, scaly papules that occur over the dorsal aspect of the metacarpophalangeal, proximal and distal interphalangeal joints, whereas Gottron's sign is the same red, scaly papular rash occurring elsewhere on the body. These cutaneous lesions typically worsen with sun exposure.

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7 **Figure 1 – Gottron’s papules over metacarpal and interphalangeal joints in a patient with DM**

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9 Reproduced with kind permission of Dermatology Online Journal

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15 **Figure 2 – Heliotrope rash over the left eyelid with associated periorbital oedema**

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17 Reproduced with kind permission of Dermatology Online Journal

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23 **Figure 3 – Mechanics hands – scaling, cracking and fissuring with bleeding along the lateral and**
24 **palmar aspects of the fingers in a patient with PM**

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26 Reproduced with kind permission of Dermatology Online Journal

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31 **Juvenile DM**

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33 Juvenile DM (JDM) has similar clinical features to adult DM and is characterised by myositis,
34 cutaneous features and systemic involvement in patients under the age of 18 years[11]. Features
35 particular to JDM include cutaneous ulcerations, calcinosis cutis and vasculopathy.
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39 **Amyopathic DM**

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41 DM can exist without myositis, this uncommon subtype is termed clinically amyopathic DM
42 (CADM)[12]. Apart from muscle involvement, the clinical features of CADM are the same as typical
43 DM, in terms of risk of ILD, cutaneous manifestations and malignancy. Hypomyopathic disease may
44 be seen in DM patients with MR or muscle biopsy evidence of myositis without weakness.
45 Confusingly, patients may also present with histological features of DM without an overt rash
46 (dermatomyositis sine dermatitis).
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52 **Anti-synthetase syndrome**

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54 The anti-synthetase syndrome is a particularly severe IIM subtype associated with myositis, ILD and
55 inflammatory symmetrical polyarthritis of the small joints of the hands and feet[13]. Marked fever,
56 Raynaud’s phenomenon and mechanics hands are also characteristic of the anti-synthetase
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3 syndrome. Anti-synthetase syndrome is defined by the presence of an anti-synthetase autoantibody
4 and ≥ 1 of the following: myositis, ILD, Raynaud's phenomenon, mechanics hands, arthritis and fever.
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8 **Immune-mediated necrotising myopathy**

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10 Immune-mediated necrotising myopathy (IMNM), a rare but severe IIM subtype, is characterised by
11 muscle necrosis and regeneration resulting in proximal muscle weakness[14]. In contrast to the
12 previously discussed IIMs, inflammatory infiltrates on muscle biopsy are not a predominant feature.
13 IMNM is commonly secondary to either statin use or malignancy. The statin-associated form of
14 IMNM is associated with autoantibodies directed against HMGCR and characteristically does not
15 improve despite withdrawal of the statin. In the cancer associated cases, treatment of malignancy, if
16 possible, can lead to resolution of the myopathy.
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20 **Inclusion body myositis**

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22 IBM is a condition characterised by both inflammatory and degenerative changes within the
23 muscle[15]. The muscle weakness pattern is notable for both proximal and distal involvement with
24 asymmetry being a common feature. The pattern of muscle weakness particular to IBM is early
25 involvement of the finger flexors, ankle dorsiflexors and knee extensors. Dysphagia is also a common
26 feature of IBM[16]. The condition follows a slowly progressive course and is unresponsive to
27 immunotherapy. High degrees of disability are seen, especially due to falls and weakness of grip.
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34 **Association with cancer**

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36 The association between the IIMs and increased risk of cancer has been well reported[17–22]. The
37 risk of cancer in the IIMs is between 2 and 7 times higher than the general population. The risk is
38 highest in DM (2-7 times higher) compared to PM (2 times higher). The risk of malignancy is highest
39 in the year prior to and the year after IIM onset. DM confers a particularly higher risk of lung, ovarian
40 and breast cancer, whereas PM is more associated with non-Hodgkin lymphomas, lung and bladder
41 cancer.
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43

44 Current cancer screening recommendations for a patient newly diagnosed with PM or DM comprise
45 comprehensive history and examination, including rectal, breast, pelvic and testicular examination.
46 Prostate specific antigen measurement should be performed in men. The increased risk of ovarian
47 cancer makes ovarian imaging via ultrasound prudent. The presence of breast cancer should be
48 investigated via mammogram. The clinical utility of further imaging via CT scan of the thorax,
49 abdomen and pelvis is not yet clarified, however this would be recommended to identify solid
50 tumours that may otherwise remain undetected. As the risk of cancer remains high up to three years
51 after IIM onset, it may be appropriate to repeat screening investigations; however studies have not
52 yet revealed the utility of this.
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Typical presentation of IIMs

Diagnosis of an IIM can be straightforward if a patient presents with typical muscle weakness, clear multisystem involvement and a consistent serological profile. However, many patients in clinical practice present with non-specific clinical features, such as fever, fatigue, myalgia and arthralgia.

Acute or subacute symmetrical muscle weakness of the proximal arm and leg muscles is typical of the IIMs. Muscle weakness may cause a patient to complain about difficulty in combing their hair or progressive difficulty in rising from a chair. Weakness of other muscle groups may cause dysphonia or dysphagia.

As previously described, a diagnosis of DM can be suspected in the presence of muscle weakness and typical DM cutaneous features.

A patient may first present with an extra-muscular manifestation of an IIM, such as ILD or Raynaud's phenomenon, therefore the IIMs should be included as a secondary cause when investigating for an underlying process.

Approach to diagnosis

A careful history should be taken to identify important information, such as family history of muscle disorders, current or past use of myopathic drugs (see Table 1), excess alcohol intake, presence of dysphagia or dysphonia.

A comprehensive examination should be carried out to identify the multitude of signs that can manifest. In particular, careful examination for DM-associated cutaneous changes and manual muscle testing should be carried out. The strength of the following muscle groups as a minimum should be quantified: deltoid, biceps, wrist extensors, quadriceps, ankle dorsiflexors, neck flexors, gluteus medius and gluteus maximus.

Recommended baseline investigations include concentration of muscle enzymes, such as CK, ALT, AST, aldolase and LDH. The concentration of CK has diagnostic and monitoring utility. Although a raised CK is sensitive for a diagnosis of an IIM, there are many other causes of a raised CK (Table 2). Patients with a myositis-spectrum disorder but no muscle disease may present with a normal CK. Less frequently, and sometimes in association with cancer-associated myositis, IIM patients with associated myopathic involvement may also not mount a raised CK response.

Pathological examination of a muscle biopsy will allow confirmation of muscle inflammation, identify IIM subtype and distinguish non-IIM forms of myopathy. It is recommended that muscle biopsies be examined in tertiary centres, due to the importance of accurate identification of features that may indicate rare or newly defined forms of myopathy.

Testing for myositis specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) can further identify clinical subtype, inform the requirement for further investigations and predict treatment response. See section on "autoantibody profiles" for more details.

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Magnetic resonance imaging (MRI) of muscle is being increasingly performed. Imaging protocols that include the fat-suppressed short tau inversion recovery (STIR) sequence are particularly helpful for identifying muscle oedema, which indicates active myositis, although is not specific. T1 weighted images may demonstrate fatty replacement of muscle and scar tissue, which indicates irreversible muscle damage.

In myopathies, EMG testing typically shows low voltage polyphasic potentials. Fibrillation is only present in the acute phase of myositis. Unfortunately, there are no myositis-specific EMG changes and interpretation can be variable due to operator dependency.

As ILD is a feature of the IIMs, particularly the anti-synthetase syndrome, pulmonary function testing and high resolution CT scanning of the lungs should be carried out. Cardiac failure due to cardiac involvement should be investigated via echocardiogram and ECG.

Differential diagnosis

Due to the variety of clinical features, age ranges of presentation and systemic features, a differential diagnosis should be considered before a diagnosis of IIM is arrived at, especially in patients without diagnostic serology. Indeed, it is not uncommon for an alternative diagnosis to become apparent months or years after a diagnosis of IIM has been made. The differential diagnoses that should be considered are listed in Table 1.

Table 1 – Causes of proximal muscle weakness other than IIM

Adapted from: Oddis CV *Rheum Dis Clin North Am* 2002, 28: 979-1001.

CTD = connective tissue disease

Table 2 – Causes of elevated CK other than active idiopathic inflammatory myopathy (IIM)

Adapted from: Targoff IN. *Rheum Dis Clin North Am* 2002, 28: 859-890.

EMG = electromyography, CNS = central nervous system, GI = gastrointestinal, CK = creatinine kinase

Autoantibody profiles

Although identifying each patient's IIM as one of the previously discussed clinical subtypes can inform prognosis, response to treatment and risk of cancer, the marked heterogeneity within each subtype limits this approach. The recent identification of a large number of certain MSAs and MAAs and the observation that clinically distinct IIM syndromes are associated with each allows for much greater investigation and treatment stratification. MSAs are highly specific and therefore their

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3 presence strongly indicates an underlying IIM. MSAs usually exist exclusively, however a small
4 minority of patients may be positive for more than one. Table 3 displays each MSA, the
5 corresponding prevalence and associated clinical features.
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10 **Table 3 – MSAs, prevalence and associated clinical features**

11 Adapted from: Betteridge Z. J Intern Med 2016;280:8–23. [23]

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13 MSA = myositis specific autoantibody, MDA5 = melanoma differentiation-associated protein 5, SAE1
14 = SUMO-activating enzyme subunit 1, TIF1 = transcriptional intermediary factor 1, SRP = signal
15 recognition particle, HMGCR = 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
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20 **MAAs**

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22 An IIM can exist alongside connective-tissue diseases and these are referred to as “overlap” cases.
23 Particular MAAs occur in overlap cases and have diagnostic utility. Although they occur more
24 frequently than the MSAs, they are also found in other connective tissue diseases, such as SLE and
25 scleroderma, thus reducing their diagnostic specificity.
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28 The anti-PMscl autoantibody occurs most commonly in patients who have PM with overlapping
29 sclerodermatous features, are mutually exclusive to MSAs and other MAAs, and are associated with
30 similar clinical features to the anti-synthetase syndrome - increased risk of ILD, mechanics hands and
31 Raynaud’s phenomenon[24].
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34 Coexisting IIM and mixed CTD is associated with positivity for anti-U1-snRNP autoantibodies, which
35 confers good response to steroid treatment and lower prevalence of myositis[25].
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38 Patients positive for the anti-Ku autoantibody are more likely to suffer Raynaud’s phenomenon, ILD,
39 arthralgia and myositis. Anti-Ku autoantibody positive patients require higher doses of
40 corticosteroids to induce myositis remission and the ILD has been shown to be particularly steroid
41 resistant[26].
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43
44 The anti-SSA and SSB autoantibodies are also associated with IIM/CTD overlap cases. A 14-25%
45 frequency of anti-SSA autoantibodies has been reported in adult PM/DM overlap cases, compared to
46 9-19% in IIM-non-overlap cases. Anti-SSA autoantibodies may co-exist with anti-Jo1 positivity, and
47 are also observed in IBM. The anti-SSB autoantibodies exist in 4-12% of overlap patients and only 2-
48 7% of IIM-non-overlap cases[27].
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52 **Classification criteria**

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54 In 1975 Bohan and Peter published their classification criteria for DM and PM (Table 4)[1,2]. These
55 criteria encompassed clinical features, muscle biopsy evidence of myositis, elevation of muscle-
56 associated enzymes, electromyographic features and the characteristic skin rashes of DM.
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3 Importantly, these criteria were devised before IBM or IMNM were recognised as distinct clinical
4 entities. Separate criteria for these conditions and anti-synthetase syndrome are now available[28].
5

6 Depending on the number of criteria fulfilled, a label of possible, probable or definite DM/PM could
7 be assigned. In an effort to include advances in IIM presentation and identification of MSAs, the
8 International Myositis Assessment and Clinical Studies (IMACS) Group are developing the
9 International Myositis Classification Criteria Project (IMCCP) classification criteria [28].
10

11 The IMCCP classification criteria will take the form of an individual's probability of having an IIM.
12 Classification as an IIM using the IMCCP criteria requires a probability higher than 50% and the cut
13 off for inclusion into a clinical trial is a probability higher than 90%.
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15

16 17 18 **Table 4 – Bohan and Peter criteria**

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20 Exclusion criteria: congenital muscular dystrophies, central or peripheral neurological disease,
21
22 infectious myositis, metabolic/endocrine myopathies and myasthenia gravis
23

24 CK = creatinine kinase, EMG = electromyogram, DM = dermatomyositis, PM = polymyositis
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27 28 **Treatment**

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30 Pharmacological management of the IIMs involves induction of remission followed by maintenance
31 of remission[29].
32
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34 **Induction of remission**

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36 Glucocorticoids still form the cornerstone of IIM remission induction. For individuals with moderate
37 disease severity, oral prednisolone at a dose of 0.5-0.75mg/kg/day (usually 40-60mg) is
38 recommended. For those with more severe disease, intravenous methylprednisolone (250-500mg in
39 2-3 doses on alternate days) can be used initially and then converted to oral prednisolone once
40 disease severity has reduced. The initial dose should be continued until the CK level is lower than
41 twice the upper limit of normal. Following adequate reduction of disease activity and CK level, the
42 daily prednisolone dose can be weaned alongside early introduction of a second line agent.
43
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45 For those patients in whom the CK does not improve after 4-5 weeks, methylprednisolone can be
46 added, if not already used, or administration of IV cyclophosphamide, IV immunoglobulin or IV
47 rituximab should be considered under specialist advice.
48
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50 **Maintenance of remission**

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52 As with other rheumatological diseases, disease modifying anti-rheumatic drugs (DMARDs) can be
53 used to maintain IIM remission and allow the dose reduction or withdrawal of glucocorticoid
54 treatment.
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3 Methotrexate (MTX), azathioprine (AZA) and mycophenolate mofetil (MMF) are effective
4 maintenance treatments for most patients, however some will remain resistant and require
5 escalation of treatment. In this situation, combination treatment with ciclosporin and MTX or
6 MTX/AZA with MMF can be effective. Treatment with tacrolimus, cyclophosphamide, rituximab or
7 tocilizumab can also be considered for more resistant cases.
8
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10 11 12 **Conclusions**

13
14 In conclusion, the IIMs are rare autoimmune connective tissue disorders characterised by distinct
15 clinical subtypes and varied multisystem involvement. Identification of MSA/MAAs can inform
16 diagnosis and risk of secondary organ involvement and cancer development. The anticipated IMCCP
17 classification criteria improve on the Bohan and Peter criteria. Treatment constitutes exclusion of
18 other causes of muscle weakness and raised CK, then use of immunosuppression with induction of
19 remission followed by maintenance.
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Table 1: Causes of proximal muscle weakness other than IIM

Inherited myopathies	Muscular dystrophies: Becker/Duchenne, facioscapulohumeral, limb girdle Congenital myopathies: nemaline, centronuclear, central core Myotonic disease: dystrophica myotonica (1&2), myotonia congenita
Neurologic	Neuropathic conditions: spinal muscular atrophies, amyotrophic lateral sclerosis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy Neuromuscular junction disorders: Eaton-Lambert syndrome, myasthenia gravis
Metabolic	Glycogen storage diseases: acid maltase deficiency (Pompe), McArdle disease Hypokalaemia Vitamin D deficiency Mitochondrial cytopathies Nutritional: vitamin D deficiency, malabsorption Other: uraemia, hepatic failure, alcoholism, acute intermittent porphyria, diabetic plexopathy
Endocrine myopathies	Hyper/hypothyroidism, acromegaly, Cushing's syndrome, Addison's disease, hyper/hypocalcaemia
Drug induced myopathies	Lipid lowering agents e.g. statins, and clofibrate; D-penicillamine, chloroquine, amiodarone, vincristine, zidovudine
Infections	Acute viral: influenza, hepatitis B, echovirus, rickettsia, coxsackie virus, rubella, vaccine-associated Bacterial pyomyositis: staphylococcus, streptococcus, clostridium perfringens, leprosy
Myositis/CTD	Parasites: toxoplasma, trichinella, schistosoma, cysticercus Myositis - overlapping with systemic sclerosis, mixed CTD,

overlap	Sjögren's syndrome, systemic lupus erythematosus and rheumatoid arthritis
Miscellaneous	Periodic paralyses, carcinomatous neuromyopathy, acute rhabdomyolysis, myositis ossificans, microembolisation by atheroma or carcinoma, sarcoidosis with myopathy

Adapted from: Oddis CV *Rheum Dis Clin North Am* 2002, 28: 979-1001.

CTD = connective tissue disease

Table 2: Causes of elevated CK other than active idiopathic inflammatory myopathy (IIM)

1. Muscle trauma

- a) Crush injury
- b) Needle stick
- c) EMG
- d) Surgery
- e) Convulsions, delirium tremens

2. Diseases affecting muscle

- a) Myocardial disease e.g. infarction
- b) Rhabdomyolysis
- c) Metabolic or mitochondrial myopathies
- d) Muscular dystrophy
- e) Infectious myositis
- g) Muscle denervation. E.g. Amyotrophic lateral sclerosis
- f) Myopathy associated Ryanodine receptor 1 (*RYR1*) gene mutations

3. Drug/toxin-induced myopathy

- a) Lipid-lowering agents, especially HMG-CoA-reductase inhibitors
- b) Alcoholic myopathy
- c) Drugs of abuse: e.g. cocaine, amphetamines, phencyclidine
- d) Malignant hyperthermia and neuroleptic malignant syndrome
- e) Other medications: e.g. zidovudine, colchicine, chloroquine, ipecac, barbiturates, morphine, diazepam

4. Drug-induced myositis

- a) D-penicillamine
- b) Interferon

5. Endocrine and metabolic abnormalities

- a) Hypothyroidism
- b) Hypokalemia
- c) Hypocalcaemia
- d) Hyperosmolar state or ketoacidosis
- e) Diabetic nephrotic syndrome with oedema
- f) Renal failure

6. Elevation of CK-BB

- a) CNS disease
- b) Tumours (GI, bronchial, other)

7. Elevation without disease

- a) Strenuous, prolonged, and/or unaccustomed exercise
- b) Ethnic group (black > white)
- c) Increased muscle mass
- d) Macro-CK
- e) idiopathic

Adapted from: Targoff IN. *Rheum Dis Clin North Am* 2002, 28: 859-890.

EMG = electromyography, CNS = central nervous system, GI = gastrointestinal, CK = creatinine kinase

Table 3 – MSAs, prevalence and associated clinical features

MSA	Prevalence	Clinical features
Anti-synthetase antibodies (Jo-1, Zo, OJ, PL12, KS, PL7, EJ, Ha)	Jo-1 9-24% in adult DM/PM Non-Jo-1 <5% in adult DM/PM 2-4% in JDM	Myositis, ILD, non-erosive arthritis, mechanics hands, Raynaud's, fever
MDA5	10-48% in Asian adults with DM 0-13% in Caucasian adults with DM	CADM Rapidly progressive ILD,

	7-38% in JDM	alopecia, skin ulceration, palmar papules, panniculitis
SAE1	Exclusive to DM	CADM, dysphagia preceding muscle weakness
Mi2	9–24% adult IIM 4–10% JDM	Marked cutaneous DM, generally favourable response to treatment
NXP2	1–17% adult PM/DM 23–25% JDM	Calcinosis in JDM
TIF1	13–31% adult PM/DM 22–29% JDM	Strong association with cancer – up to 69%
SRP	5% Caucasian adults PM/DM 8–13% Asian/African adult PM/DM <2% JDM	Severe necrotising myopathy, dysphagia Lower risk of ILD
HMGCR	6% adult PM/DM <1% JDM	Necrotising myopathy Statin use
cn1A	33–34% IBM 36% Sjogren's syndrome 20% SLE 0-5% adult DM/PM	IBM – moderate specificity

Adapted from: Betteridge Z. J Intern Med 2016;280:8–23. [23]

MSA = myositis specific autoantibody, MDA5 = melanoma differentiation-associated protein 5, SAE1 = SUMO-activating enzyme subunit 1, TIF1 = transcriptional intermediary factor 1, SRP = signal recognition particle, HMGCR = 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase

Table 4 – Bohan and Peter criteria

1	Symmetrical weakness of limb-girdle muscles and anterior neck flexors
2	Muscle biopsy evidence typical of myositis
3	Elevation of serum skeletal muscle enzymes, particularly CK
4	Typical EMG features of myositis
5	Typical DM rash, including heliotrope and Gottron's papules
For the diagnosis of PM:	
For the diagnosis of DM:	

Definite:	All of items 1-4	Definite:	Item 5 plus 3 of items 1-4
Probable:	3 of items 1-4	Probable:	Item 5 plus 2 of items 1-4
Possible:	2 of items 1-4	Possible:	Item 5 plus 1 of items 1-4

Exclusion criteria: congenital muscular dystrophies, central or peripheral neurological disease, infectious myositis, metabolic/endocrine myopathies and myasthenia gravis

CK = creatinine kinase, EMG = electromyogram, DM = dermatomyositis, PM = polymyositis

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Figure 1 – Gottron’s papules over metacarpal and interphalangeal joints in a patient with DM

231x136mm (96 x 96 DPI)

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Figure 2 – Heliotrope rash over the left eyelid with associated periorbital oedema

270x180mm (96 x 96 DPI)

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Figure 3 – Mechanics’ hands – scaling, cracking and fissuring with bleeding along the lateral and palmar aspects of the fingers in a patient with PM

219x146mm (96 x 96 DPI)

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