Idiopathic inflammatory myopathies

When to suspect one and what to do about it

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This rare group of autoimmune diseases characteristically presents as painless, progressive proximal muscle weakness with a raised creatine kinase level but can also manifest in many other ways. It is important for GPs to recognise them because, without prompt treatment, a patient's condition can rapidly deteriorate, resulting in permanent organ damage or death.

The idiopathic inflammatory myopathies (IIMs), collectively often shortened to the less accurate term 'myositis', are a group of rare autoimmune diseases that typically result in skeletal muscle inflammation but can have a wide range of associated extramuscular manifestations. The diagnosis is often difficult and therefore delayed; it relies heavily on clinical assessment, although diagnostic tools are improving. Without prompt treatment, a patient's condition can deteriorate quickly and lead to permanent organ damage or worse.

KEY POINTS

- The idiopathic inflammatory myopathies (IIMs) include polymyositis, dermatomyositis, inclusion body myositis and a growing number of other subtypes.
- The IIMs are individually rare but serious chronic conditions that can affect patients at any age and have substantial associated morbidity and mortality.
- The characteristic clinical presentation is painless, progressive proximal muscle weakness and a raised creatine kinase level.
- The differential diagnosis of weakness and/or a raised creatine kinase level is extensive, and specialist referral is warranted once more common conditions, such as endocrine disorders or drug-related causes, are excluded.
- The IIMs can cause a broad range of extramuscular organ manifestations, such as rash, interstitial lung disease, symptoms of Raynaud's syndrome, dysphagia and arthritis.
- A careful clinical assessment is central to making a diagnosis but diagnostic tools, such as novel autoantibody tests, are improving.
- There are no treatment guidelines, but most patients with IIMs will receive corticosteroids and an additional immunosuppressive agent.
- GPs are ideally placed to assist with many aspects of the patient's management, such as monitoring blood pressure, weight gain, bone density loss and blood glucose and lipid levels and ensuring all recommended cancer screening is up to date.

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TABLE 1. DIFFERENTIAL DIAGNOSES IN A PATIENT PRESENTING WITH WEAKNESS WITHOUT PROMINENT SENSORY SIGNS

Diagnostic category	Differential diagnosis
Drug- or toxin-related	Corticosteroids, statins,* colchicine,* antiretrovirals,* alcohol,* antimalarials*
Endocrinopathy	Hyper- or hypothyroidism,* osteomalacia, Cushing's syndrome, Addison's syndrome, acromegaly
Neuromuscular junction	Myasthenia gravis, Lambert–Eaton myasthenic syndrome
Neuropathy	Motor neurone disease, diabetic amyotrophy or plexopathy
Inherited	Muscular dystrophies,* myotonic dystrophies,* channelopathies*
Metabolic	Mitochondrial myopathies,* glycogen storage disorders,* fatty acid oxidation defects*
Infective	HIV,* acute viral or bacterial infections*
Miscellaneous	Sarcoidosis,* amyloidosis,* neuroleptic malignant syndrome,* chronic graft versus host disease*

* These conditions are usually also associated with an elevated creatine kinase level (see Table 4).

Encouragingly, both our understanding of these diseases and therapeutic advances have been progressing rapidly, but the overall mortality for patients with IIM remains more than threefold higher than for their age- and sex-matched peers.[1] This article outlines when to suspect an IIM, what differential diagnoses to consider and how investigations can help to reduce uncertainty before involving a specialist.

What are the idiopathic inflammatory myopathies?

Since the first widely accepted classification of IIMs was proposed in 1975, the terms polymyositis and dermatomyositis have become well established and familiar in clinical practice. Knowledge of IIMs has now moved beyond this simplistic dichotomous classification, as contemporary research has recognised well-defined phenotypes within these groups and established that some IIMs predominantly affect organs rather than skeletal muscles, and especially because of widespread access to novel autoantibody tests. Terms such as antisynthetase syndrome, immune-mediated necrotising myopathy, amyopathic dermatomyositis, inclusion body myositis and overlap myositis are now becoming well known. Detailed discussion of these IIM subtypes is available elsewhere but, for practical purposes, it is most important to be aware that these terms are all interrelated and describe conditions that share many similarities.[2,3]

How often do they occur and who do they affect?

IIMs are rare, with a recent estimate of incidence in South Australia of eight per million person-years.[4] This figure is in keeping with estimates from other regions; a systematic review of IIM epidemiological studies conducted around the world found a mean incidence of eight per million person-years and a prevalence of 14 per 100,000 people.[5]

As with most autoimmune diseases, the exact aetiology of IIMs remains elusive but they are thought to represent an interaction of genetic influences with environmental factors. IIMs can affect people at any stage of life, from children (the disease is known as juvenile polymyositis or dermatomyositis in those under the age of 18 years) to the elderly. They affect women more often than men.[5] Some interesting associations have been found, such as:

- between decreased latitude (living closer to the equator) and an increased risk of dermatomyositis, which is thought to be mediated by increased ultraviolet radiation exposure
- between smoking and antisynthetase syndrome
- between genetic polymorphisms and the very rare statin-associated immune-mediated necrotising myopathy (see 'Statin-associated idiopathic inflammatory myopathy' below).[6-8]

There are many more differences than similarities in the pathogenic mechanisms implicated in IIM subtypes, which is surprising given their many shared manifestations.

How do they present and when should they be suspected?

Weakness

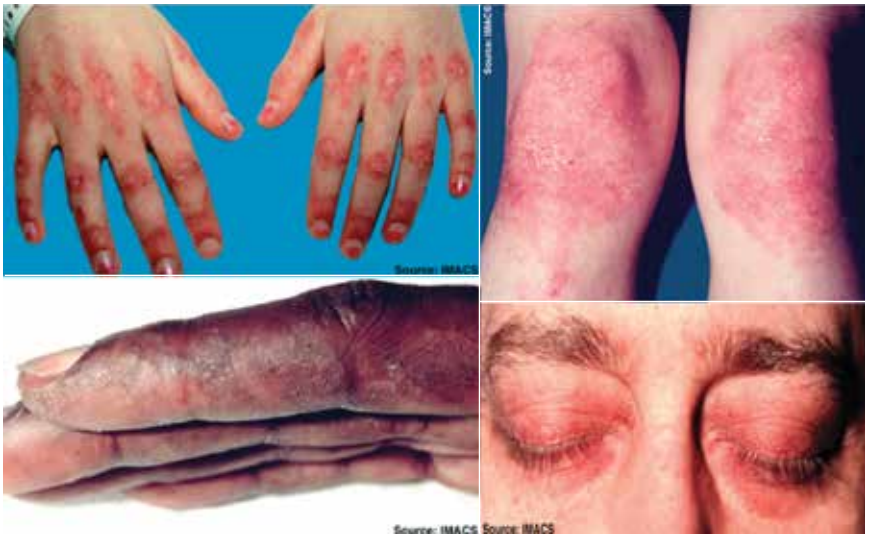
A typical presentation of IIM would be a patient complaining of painless, progressive proximal muscle weakness, although patients rarely volunteer the pattern of their weakness and often underestimate the extent of it. The clues are usually to be found in the functional impact: patients are unable to get out of a low-seated chair (such as a car seat) without using their arms or they struggle to climb stairs, wash their hair or reach into high cupboards. Muscle pain (myalgia) is not usually prominent and, if present, suggests an alternative diagnosis in most cases.

Although not typical, some IIMs (particularly the subtype of inclusion body myositis) can also cause distal muscle weakness. In this case, patients may notice problems like difficulty with grip when holding shopping bags or watchstraps becoming loose (because of muscle wasting). Other patients may present with axial muscle weakness, describing problems lifting their head from a pillow, having the stooped posture of camptocormia (which is correctable when lying flat,

unlike with most other causes of this appearance) or even presenting with symptoms of hypoventilation (such as morning headaches or somnolence), suggesting respiratory muscle weakness. IIMs should always be part of the differential diagnosis in these circumstances, but a broad range of other conditions could be implicated (Table 1). It is particularly important to consider easily remediable systemic causes of weakness, such as electrolyte disturbance and thyroid disease.

Extramuscular manifestations

Extramuscular manifestations may instead be the predominant feature, especially early in the disease. IIM should therefore also be considered as a differential diagnosis in a wide range of other circumstances, as outlined below.



Figures 1a to d. Cutaneous manifestations of idiopathic inflammatory myopathy. a (top, left). Gottron's papules. b (bottom, left). Mechanic's hands. c (top, right). Gottron's sign. d (bottom, right). Heliotrope rash.

Adapted with permission from Dugan EM, et al; International Myositis Assessment and Clinical Studies Group (IMACS). Dermatol Online J 2009; 15 (2): 1.[9]

Rash

There are many potential cutaneous manifestations of IIM.[9] Those that are particularly important to recognise, because they are so suggestive of IIM, are the appearances of Gottron's papules; the so-called mechanic's hands; the dusky erythematous patches on the extensor surfaces of the elbows, hips and knees known as Gottron's sign; and the periorbital 'heliotrope' rash (Figures 1a to d).

Breathlessness

The biggest single contributor to morbidity and mortality in patients with IIM is not the muscle disease but the presence of interstitial lung disease.[10] Affected patients typically complain of a progressive breathlessness on exertion, usually without a cough. Interstitial lung disease occurs in as many as 90% of patients with IIM, in whom it can closely mimic other less treatable causes, such as idiopathic pulmonary fibrosis.[10]

Swallowing difficulty

Dysphagia, as a result of either pharyngeal muscle involvement (patients complaining of 'choking') or more distal oesophageal dysmotility (patients 'getting food stuck' or regurgitating food), is also relatively frequent in IIM. It can progress quickly and be slow to abate, with some patients requiring long-term percutaneous endoscopic gastrostomy feeding.

Raynaud's syndrome

New-onset symptoms of Raynaud's syndrome, especially in an adult, should always ring alarm bells about connective tissue diseases, such as systemic sclerosis and mixed connective tissue disease. They can also be a feature of IIM, particularly antisynthetase syndrome. An added level of diagnostic difficulty can arise because patients with antisynthetase syndrome often have negative antinuclear antibody test results, which may deter the clinician from making a diagnosis of an autoimmune condition.[11]

Inflammatory arthritis

Some of the IIMs are associated with a nonerosive symmetrical polyarthritis, typically of the small joints, that can mimic other more common conditions, such as rheumatoid arthritis.[3]

Palpitations or heart failure

The IIMs have been found to involve almost all components of the cardiorespiratory system, with myocarditis, pericarditis, conduction system abnormalities and pulmonary hypertension being the most common manifestations. Although there are many other more common causes of these conditions, IIMs should be considered and investigated, especially if there are any other relevant clinical features as detailed above.[12]

Which tests help make the diagnosis?

In an age of ever more complex and often expensive investigations, a careful clinical assessment remains central to making a diagnosis of IIM. A suggested assessment structure is summarised in Table 2. This will greatly enhance the interpretation of results of subsequent investigations, none of which approach perfect sensitivity or specificity for IIM; they are simply the best tools available to support the clinical impression or refute relevant differential diagnoses. Table 3 details the investigations that should be considered. Even without

TABLE 2. TYPICAL HISTORY AND EXAMINATION FINDINGS IN A PATIENT WITH AN IDIOPATHIC INFLAMMATORY MYOPATHY

Clinical system	History	Examination
Locomotor	Weakness (usually painless); impaired physical function (difficulty getting out of chair or bed, falls, head drop, impaired activities of daily living); arthralgia or arthritis	Muscle weakness (proximal more than distal) and wasting; neck weakness (flexion more than extension); camptocormia; 'waddling' gait; synovitis
Cardiorespiratory	Breathlessness on exertion; cough; orthopnoea (implying respiratory muscle involvement or congestive cardiac failure); symptoms of carbon dioxide retention	Signs of pulmonary fibrosis and/or respiratory failure; dysphonia; arrhythmia or signs of congestive cardiac failure
Gastrointestinal	Dysphagia (with pharyngeal and/or distal oesophageal characteristics); altered bowel habit; weight loss	Unusual to have specific findings except features of malnutrition
Cutaneous	Photosensitivity; new rash; cutaneous ulcers	Rash on extensor surfaces, scalp, face (especially 'heliotrope' distribution), chest and back; calcinosis

these tests, prompt referral to a specialist with experience in the relevant area (usually a rheumatologist, neurologist or respiratory physician but could also be a dermatologist or other physician depending on organ-specific manifestations) is encouraged when there is any concern that a patient may have an IIM.

TABLE 3. SUGGESTED INVESTIGATIONS IN PRIMARY CARE WHEN AN IDIOPATHIC INFLAMMATORY MYOPATHY IS SUSPECTED

	Investigation category	Specific investigations
Core recommended investigations	Blood tests	Full blood count; urea and electrolytes (including Ca^{2+} and Mg^{2+}); liver and thyroid function tests; 25-hydroxyvitamin D; creatine kinase; ESR; CRP
	Radiological investigations	Chest x-ray
	Cardiac investigations	ECG
Additional investigations to consider	Blood tests	Immunological tests (ANA, ENA, anti-dsDNA, ANCA, RF, anti-CCP, MSA and MAA); troponin I
	Radiological investigations	High-resolution CT scan of chest (if respiratory symptoms); cross-sectional imaging if malignancy suspected
	Organ-specific investigations (if relevant)	
	Respiratory	Pulmonary function tests
	Cardiac	Echocardiogram
	Gastrointestinal	Endoscopy; swallow assessment
	Dermatological	Skin biopsy

Abbreviations: ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; CCP = cyclic citrullinated peptide; CK = creatine kinase; CRP = C-reactive protein; dsDNA = double-stranded DNA; ENA = extractable nuclear antibodies; ESR = erythrocyte sedimentation rate; MAA = myositis-associated antibodies; MSA = myositis-specific antibodies; RF = rheumatoid factor.

Creatine kinase level (and other muscle enzymes)

Creatine kinase (CK) is a key enzyme involved in energy production in muscle cells, and an increased CK level in the bloodstream is a sensitive marker for muscle injury of any cause. However, there are many possible causes of an elevated CK level (ranging from an individual's normal variant level to myocardial infarction) and the levels correlate poorly with IIM disease activity. As a raised CK level is a common clinical problem and IIM is a much less frequent cause of it than many other possibilities, several differential diagnoses to consider are shown in Table 4.

Levels of alanine transaminase and aspartate transaminase – traditionally considered to be 'liver enzymes' – are also increased in the sera of patients with muscle injury. Consequently, some patients with apparently deranged liver function test results have undergone fruitless and invasive liver biopsy before the CK level is checked and a muscle disorder suspected. Troponin T is expressed by immature and regenerating skeletal muscle fibres, as well as cardiomyocytes, and its level will therefore often be elevated in patients with active IIM. The cardiac- specific troponin I is a more appropriate screening blood test, where available, for investigating cardiac involvement in IIM.[12]

Myositis autoantibodies

There are an ever-increasing range of autoantibodies available in commercial assays that can be helpful in identifying IIM, especially for identifying the subtype and phenotype. These are shown in Table 5 and further information is available elsewhere.[11]

Malignancy screening

It is widely appreciated that IIMs have an association with malignancy. About 10% of IIMs are felt to be 'cancer-associated' and in these cases treatment targeted at the cancer usually results in effective treatment of the IIM. Men over the age of 50 years with dermatomyositis are the group at highest risk of malignancy.[13]

In practice, an open mind regarding malignancy should be maintained when investigating all patients with a possible IIM, and screening should be performed based on individual patient factors. Although these investigations will often be arranged by the specialist, it is important for the GP to ensure that all age-relevant recommended cancer screening (e.g. bowel, breast, cervical cancer) is up to date.

Other investigations

Electromyography with nerve conduction studies to exclude neuropathic conditions, muscle MRI and muscle biopsy can be valuable diagnostic tools and are often performed. These investigations would usually be considered and ordered after review by a specialist, who would not expect them to have been organised before referral.

What treatments are likely to be used?

There are no nationally or internationally accepted treatment guidelines for IIMs and very few agents with specific indications for treating them. Clinicians must therefore weigh up the existing and evolving evidence for treatments with patient-specific factors to make treatment decisions.

TABLE 4. CAUSES TO CONSIDER WHEN EVALUATING AN ELEVATED CREATINE KINASE LEVEL

Broad category	Examples
Muscle trauma	Surgical or accidental injury; limb compartment syndromes; seizures; delirium tremens
Diseases primarily affecting skeletal muscle	Rhabdomyolysis; infectious myositis; idiopathic inflammatory myopathies; metabolic myopathies; mitochondrial myopathies; dystrophinopathies; neuromyotonias
Other neuromuscular diseases	Motor neurone disease; muscle denervation from any cause (e.g. radiculopathy); spinal muscular atrophy
Drug- or toxin-induced myopathy	Use of lipid-lowering agents (especially statins); alcohol; colchicine; zidovudine; chloroquine; cocaine or amphetamines; malignant hyperthermia
Diseases of other organ systems	Myocardial infarction (or any cause of myocardial injury); stroke; hypo- and hyperthyroidism; electrolyte disturbance (hypokalaemia, hypocalcaemia, etc); hyperosmolar state or ketoacidosis; renal failure
Elevation of creatine kinase level without disease	Strenuous, prolonged and/or unaccustomed exercise; ethnic variation (e.g. higher levels in Afro-Caribbean people); high muscle mass; macrocreatine kinase

Corticosteroids (at doses up to 1 mg/kg of prednisolone or equivalent) form the backbone of most remission induction strategies. As most patients will relapse if corticosteroids are used in isolation, additional immunosuppression, which will also act as a steroid-sparing agent, should be introduced early. Typical choices include methotrexate, mycophenolate, azathioprine and tacrolimus. These agents can be used in combination in patients who do not achieve complete remission or in whom it is difficult to withdraw corticosteroids.

Various other treatments, including cyclophosphamide, rituximab and intravenous immunoglobulin, are used for patients who prove refractory to initial treatments or who have presented with organ- or life-threatening manifestations. There are numerous ongoing and planned trials into novel treatment options, which are likely to change the treatment landscape over the coming years. A more detailed discussion of the available treatments and evidence for them can be found elsewhere.[14]

What is the role of the GP in management?

The IIMs are complex and chronic diseases and GPs are an important part of the management team. Depending on the disease manifestations and internal organ involvement, a patient may be seeing more than one specialist and allied healthcare provider, and a chronic care plan is useful to co-ordinate this.

The decisions about treatments, especially those to do with pharmacotherapy and immunosuppression, will usually be guided by the specialists involved. However, there are many equally important aspects of management in which GPs and other healthcare providers are better placed to help their patients including the following.

- Evidence is emerging of the

TABLE 5. MYOSITIS-SPECIFIC AND MYOSITIS-ASSOCIATED AUTOANTIBODIES

Category	Subtype	Autoantibodies
Myositis-specific antibodies	ASS-specific	Anti-Jo-1, anti-PL-12, anti-PL-7, anti-OJ, anti-EJ, anti-KS, anti-Zo, anti-Ha
	DM-specific	Anti-Mi-2, anti-MDA-5, anti-NXP2, anti-TIF1, anti-SAE
	IMNM-specific	Anti-SRP, anti-HMGCR
Myositis-associated antibodies	NA	Anti-Ro52, anti-Ro60, anti-PM/Scl, anti-La, anti-dsDNA, anti-Sm, anti-U1-RNP, anti-Ku

Abbreviations: ASS = antisynthetase syndrome; DM = dermatomyositis; IMNM = immune-mediated necrotising myopathy; NA = not applicable.

importance of physical activity in patient outcomes.[15]
- There is almost always a need for strategies to monitor and minimise treatment-related toxicity.
- Many patients have significant physical and psychological morbidity that benefits from holistic input in the community.

Therefore, referral to allied healthcare providers to assist with exercise, physical activity, weight control and psychological support is an important component of care for many patients.

High doses of glucocorticoids (both parenteral and oral) are almost invariably required for lengthy periods, and monitoring blood pressure, weight gain, bone density loss, blood glucose levels and lipid levels are important adjuncts. Facilitating smoking cessation is essential.

Statin-associated idiopathic inflammatory myopathy

Musculoskeletal adverse events have been attributed to the use of statins, although the reasons for these symptoms are complex.[16] Most muscle-specific adverse events related to statin therapy are not primarily immune-mediated and therefore separate to the topic of IIMs. However, in the past decade, a very rare IIM syndrome – an immune-mediated

necrotising myopathy subtype – has been described as being more common in patients exposed to statins and associated with anti-HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) antibodies, the enzyme target of statin medications.

Treatment of this condition is broadly similar to the treatment of IIM described above, accompanied by a recommendation for permanent cessation of statins, although no study to date has compared outcomes in patients who cease or continue taking statins. This rare condition should be suspected in a patient taking statins who presents with weakness and a significantly elevated CK level (typically greater than 10 times the upper limit of normal) without an alternative cause, and in whom statin cessation does not result in rapid improvement in clinical or biochemical parameters.

Conclusion

The IIMs are rare but important conditions that can present in many ways, depending on the organ-specific disease manifestations. Clinical assessment involves considering a large list of differential diagnoses, and none of the available investigations is without its drawbacks. However, the most important step in identifying an IIM and organising prompt referral is suspecting it in the first place. An IIM should be strongly suspected in patients presenting with progressive proximal weakness and a raised CK level but should also be considered in patients presenting with late-onset Raynaud's syndrome symptoms, interstitial lung disease, a rash or dysphagia, among the other manifestations described here. Treatments and patient outcomes are improving rapidly, but without early intervention, patients with IIM will continue to progress to severe permanent morbidity or mortality. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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