Idiopathic inflammatory myopathies

Matthew JS Parker
James B Lilleker
Mark E Roberts
Hector Chinoy

Abstract

Idiopathic inflammatory myopathies represent a rare group of diseases characterized by a central role of autoimmune processes and the inflammation of skeletal muscle. There has been significant recent progress in understanding disease pathogenesis, phenotyping subtypes of disease and investigating effective therapeutic options. Patients typically present with progressive, proximal weakness and functional impairment, and elevated muscle enzymes. There can also have extramuscular manifestations, including skin, respiratory, articular, gastrointestinal and cardiovascular involvement, which can precede or occur in the absence of clinically detectable muscle involvement. There are therefore a multitude of potential differential diagnoses to consider. A conscientious initial evaluation supported by pragmatically structured investigations remains critical to accurate diagnosis and appropriate management of these complex conditions.

Keywords Autoantibodies; dermatomyositis; diagnosis; drug therapy; MRCP; myositis; polymyositis; prognosis

Key points

- Idiopathic inflammatory myopathies (IIM) are characterized by symmetrical inflammatory involvement of the proximal skeletal muscles
- Extramuscular manifestations include cutaneous, gastrointestinal, articular, pulmonary and cardiovascular involvement
- Serum autoantibodies are useful in identifying particular IIM subtypes and are helping in the further investigation of pathogenesis
- Current pharmacological treatments are directed at a range of immunological targets, although non-inflammatory pathways can also be important in causing muscle weakness and consequent disability

Introduction

The term 'idiopathic inflammatory myopathies' (IIM) refers to a group of rare clinico-pathological syndromes characterized by inflammatory damage to skeletal muscle, hence the more commonly employed but less specific synonym 'myositis'. However, there are often a range of additional multisystem manifestations, and extramuscular manifestations can occur in the absence of skeletal muscle inflammation. Research into these conditions is rapidly advancing understanding, and this review is intended as a clinically focused integration of the currently relevant literature.

Aetiology, pathogenesis and risk factors

Much work has been done to accurately describe the cause of IIM, but a complete understanding has proven elusive. Current working models include the interaction of predisposing genetic influences with largely obscure environmental factors.

Worthy of particular mention is the increased frequency of anti-Jo-1 antibodies in patients who are current or previous smokers, and the increased risk of developing anti-HMGCR antibody positive immune-mediated necrotizing myopathy (IMNM) in patients with HLA-DRB1:11*01 who are taking statins. Other observations include an increased incidence of dermatomyositis (DM) in low-latitude areas (closer to the equator), probably because of increased ultraviolet light exposure. There are also reported associations after exposures such as infections, drugs, vaccines, medical devices, physical exertion and emotional stress.

The strongest genetic associations identified so far are concentrated in the major histocompatibility complex (MHC) on chromosome 6. These, when combined with identification of disease-specific serum autoantibodies and typical muscle histopathological findings of inflammatory cell infiltrates and upregulated MHC expression, helps to corroborate the central role of autoimmune processes. Although the clinical features of the various IIM subtypes show considerable overlap, the aberrant pathogenic pathways implicated (including type I interferon pathways, protein transcription, translation and post-translational processes, and altered B and T cell function) can be strikingly different.[1]

Epidemiology

The rarity of the IIM and variability of classification methods make their epidemiology challenging to study and to compare

Matthew JS Parker *MBChB MRCP FRACP Clinical Research Fellow, Rheumatology Department, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, UK. Competing interests: none declared.*

James B Lilleker *MBChB (Hons) MRCP Clinical Research Fellow, The National Institute for Health Research Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, The University of Manchester, UK. Competing interests: none declared.*

Mark E Roberts *BSc MBChB FRCP MD Consultant Neurologist, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK. Competing interests: none declared.*

Hector Chinoy *PhD FRCP BMBS MSc BMedSci Honorary Consultant Rheumatologist and Senior Clinical Lecturer, Rheumatology Department, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, UK and University of Manchester, UK. Competing interests: none declared.*

over time or between populations. However, IIM have been described globally and can be considered ubiquitous. Taken collectively, a systematic review estimates the annual incidence of IIM to be 7.98 per million and the prevalence to be 14 per 100,000 persons. There is a general female predominance, with a bi-modal distribution of disease onset in childhood and then in the fifth and sixth decades.

Nomenclature and classification criteria

Our understanding of IIM has changed considerably over the last few decades. The most widely applied criteria of Bohan and Peter importantly made the distinction between DM and polymyositis (PM). These criteria were updated in various forms to also discriminate patients with inclusion body myositis (IBM), a subtype of myositis not amenable to immunosuppression. Others have incorporated the now widely available myositis-specific autoantibodies (MSAs; see below) or particular discriminating histological findings to generate criteria. A long-running international project (International Myositis Classification Criteria Project) currently has a list of classification criteria undergoing review.

Varying nomenclature of IIM subtypes is encountered in the literature and clinical practice; for adult disease, the groups include DM, anti-(tRNA)-synthetase syndrome, IMNM, IBM, myositis with overlap features and PM.

Autoantibodies

One of the most exciting recent developments has been the identification of a range of novel serum autoantibodies in IIM, many of which can be linked to different phenotypes and outcomes. Autoantibodies can now be identified in a large majority of patients with IIM and can be of great help in the initial work-up as well as in providing clues for further research into pathogenic mechanisms. Table 1 lists the relevant autoantibodies; it is beyond the scope of this article to describe their individual significance in more detail, so readers are directed to Betteridge and McHugh's review.[2]

Autoantibodies are traditionally separated into MSAs and myositis-associated autoantibodies (MAAs). The latter are present in around 20% of patients and have a lower positive predictive value or indicate another related co-morbid (or 'overlap') autoimmune rheumatic condition (e.g. systemic sclerosis, mixed connective tissue disease).

MSAs and MAAs

Autoantibodies relevant to IIMs

MSAs	
• Anti-synthetase antibodies	Anti-Jo-1, -PL-12, -PL-7, -OJ, -EJ, -KS, -Zo, -Ha
• DM-specific	Anti-Mi-2, -MDA-5, -NXP2, -TIF1, -SAE
• IMNM-specific	Anti-SRP, -HMGCR
MAAs	Anti-Ro52, -Ro60, -PmScl, -La, -dsDNA, -Sm, -U1-RNP, -Ku, -cN-1A

Table 1

Clinical features

Although muscle disease is implicit in the diagnosis of myositis, the extent of muscle disease can be highly variable, and a range of other organ systems can be involved. These should be actively investigated when considering an individual patient. A summary of typical findings is provided in Table 2.

Skeletal muscle – IIM typically cause a symmetrical proximal distribution of weakness with elevated muscle enzymes or proteins (including creatine kinase (CK), lactate dehydrogenase, alanine aminotransferase and troponin T). There are also typical electromyography (EMG) findings, myoedema on magnetic resonance imaging (MRI) and evidence of an inflammatory infiltrate with muscle damage on biopsy.

Cutaneous – a wide variety of different skin manifestation can be present and are usually helpful in identifying the IIM subset of DM. These include the widely appreciated pathognomonic Gottron's papules (or sign) over the extensor surface of the fingers, the heliotrope rash over the eyelids and the so-called 'shawl' or 'holster' signs (Figure 1). In clinical practice, the range of abnormalities is much more varied; readers are directed to an excellent review of the topic for further discussion.[3]

Gastrointestinal – dysphagia is present in around one-third of IIM, especially in the subtypes of anti-synthetase syndrome and IBM. When present, dysphagia is responsible for a large burden of morbidity and a substantial proportion of direct disease-related mortality. It is also one of the most treatment-resistant manifestations.

Articular – when present, joint involvement usually takes the form of a symmetrical small joint, typically non-erosive polyarthritis. This is more frequent in patients who have myositis with an overlap connective tissue disease or have anti-synthetase syndrome.

Pulmonary – interstitial lung disease is present in many patients with IIM and is the most common cause of disease-related death.[4] In particular, it is common in anti-synthetase syndrome, detected in as many as 90% of individuals with anti-Jo-1 antibodies; sometimes it is the only clinical manifestation, especially in those with anti-PL-12 and anti-PL-7 antibodies.

Cardiovascular – significant confusion can occur when assessing patients for cardiac involvement with IIM as troponins (and other traditionally considered 'cardiac enzymes') are also components of the myocyte and are released when skeletal muscle is damaged. In particular, troponin T is expressed by regenerating myocytes and is elevated in active myositis; cardiac-specific troponin I is more discriminating. Despite this common dilemma, true cardiac involvement in the form of atrioventricular conduction defects, tachyarrhythmias, myocarditis and heart failure is described and more common in, for example, individuals with anti-SRP antibody positive IMNM.

This is not an exhaustive description of the extramuscular manifestations of IIM, and any new symptom should prompt an open investigation into the potential involvement of other systems. In particular, approximately 10% of IIMs are associated with malignancy. This is most prevalent in older men with DM, and when specific autoantibodies, particularly against TIF1-γ (transcriptional intermediary factor-1-γ), NXP-2 (nuclear matrix protein-2) and SAE (small ubiquitin-like modifier activating enzyme), are present. Screening for occult malignancy