Pathology and Biology of Inflammatory Myopathies

The idiopathic inflammatory myopathies (IIMs) are an important heterogenous group of potentially treatable acquired disorders. On the basis of clinical, histological and immuno-pathogenetic features, three distinct subsets are recognised: dermatomyositis (DM), polymyositis (PM) and sporadic inclusion-body myositis (IBM). An accurate diagnosis is important, given the potential toxicity associated with the immunotherapy used to treat these disorders. A wide array of histochemical and immunocytochemical stains are used to investigate cases. This review outlines the clinical features, pathology and recent advances in the pathogenesis and treatment of IIMs, with a special emphasis on the role of muscle biopsy in their diagnosis and management.

Clinical features and laboratory investigations

There are differences in the clinical features of the three major forms of inflammatory myopathy (Table 1). A clinical diagnosis of an inflammatory myopathy is confirmed by serological tests, electromyography and a muscle biopsy. Autoantibodies are found in up to 20% of patients in PM and DM but are unusual in IBM (Table 2). With the possible exception of anti-Jo-1, none of the autoantibodies have sufficient specificity or sensitivity to be of diagnostic value. Autoantibodies in IBM are unusual. They are not associated with muscular dystrophies or metabolic myopathies, although their presence should not automatically exclude these diagnoses. The most sensitive muscle enzyme assay is creatine kinase (CK), which is increased up to 50 times in active disease. In IBM, CK is more mild-enzyme assay is creatine kinase (CK), which is increased up to 50 times in active disease. In IBM, CK is more mildly elevated. Enzyme activity can be normal in some cases. This review outlines the clinical features, pathology and recent advances in the pathogenesis and treatment of IIMs, with a special emphasis on the role of muscle biopsy in their diagnosis and management.

Muscle biopsy

A definitive diagnosis of idiopathic inflammatory myopathies requires a muscle biopsy. The criteria as originally proposed by Bohan and Peter in 1975 have been more recently modified to include histological differences between PM, DM and IBM.

Technical considerations

The biopsy should ideally be performed before commencing treatment. Where the distribution of weakness is proximal, a moderately affected proximal muscle that is also easily accessible, such as the quadriceps (vastus lateralis) or the biceps can be selected. There are advantages in limiting the biopsies to these muscles as their normal distribution of fibre sizes and fibre types is well recognised. A muscle that is severely atrophied or has been subjected to electromyography should not be biopsied. Open biopsy or needle biopsy may be performed, the latter are smaller but are often adequate for diagnostic purposes. Sufficient tissue must be obtained for light microscopic, histochemical, immunohistochemical, electron microscopic and biochemical evaluation. All histological, histochemical and immunohistochemical studies are best demonstrated on unfixed material.

Pathological features

Although the underlying pathogenesis in PM, DM and IBM is different, they have several pathological features in

Table 1: Clinical features in inflammatory myopathies

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<tr>
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<th>DM</th>
<th>PM</th>
<th>IBM</th>
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<tbody>
<tr>
<td>Age</td>
<td>Children (juvenile DM) and adults</td>
<td>Adults, mainly after the second decade</td>
<td>Adults, mainly over 50 years</td>
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<tr>
<td>Sex</td>
<td>Females &gt; Males</td>
<td>Females &gt; Males</td>
<td>Males &gt;&gt; Females</td>
</tr>
<tr>
<td>Onset</td>
<td>Subacute (several weeks), can be acute</td>
<td>Subacute (typically over months)</td>
<td>Chronic (over years)</td>
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<td>Muscle involvement</td>
<td>Weakness proximal, symmetric, non-selective</td>
<td>Weakness proximal, symmetric, non-selective</td>
<td>Weakness asymmetric, typically involves quadriceps and long finger flexors first</td>
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<tr>
<td>Skin rash</td>
<td>Characteristically present, rarely transient or absent</td>
<td>Absent</td>
<td>Absent</td>
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<td>Extramuscular manifestations</td>
<td>Joint contractures, subcutaneous calcinosis and ischaemic bowel disease in juvenile DM. Increased association with malignancy in adults</td>
<td>Cardiac involvement and interstitial lung disease particularly associated with anti-Jo-1 antibody</td>
<td>Infrequent</td>
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<td>Association with connective tissue disease</td>
<td>Up to 12% with scleroderma and mixed connective tissue disease</td>
<td>5-8% with lupus, less commonly Sjögren’s and rheumatoid arthritis</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>Yes</td>
<td>Yes</td>
<td>Progressive disease with poor response to treatment</td>
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Table 2: Autoantibodies in inflammatory myopathies

<table>
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<tr>
<th>Autoantibody</th>
<th>Characteristics</th>
<th>Associations</th>
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<tr>
<td>anti-Jo-1</td>
<td>anti-histidyl-tRNA synthetase antibody (80% of all anti-synthetases)</td>
<td>interstitial lung disease in PM/DM</td>
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<tr>
<td>anti-Mi-2</td>
<td>anti-signal recognition particle (nuclear helicase)</td>
<td>10-15% of DM and PM</td>
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<td>anti-polymyositis-Scl</td>
<td>anti-signal recognition particle (nuclear complex)</td>
<td>DM with scleroderma</td>
</tr>
<tr>
<td>anti-KL6</td>
<td>anti-signal recognition particle (mucin-like glycoprotein)</td>
<td>interstitial lung disease in PM/DM</td>
</tr>
<tr>
<td>anti-nRNP</td>
<td>anti-nuclear ribonucleoprotein</td>
<td>Overlap with mixed connective tissue disease</td>
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common. In all IIMs variation in fibre diameters is often seen, but hypertrophy is less pronounced compared to the muscular dystrophies. Large group atrophy and fibre type grouping is absent. Scattered necrotic fibres are common.

Features of DM include perifascicular atrophy (Figure 1), defined as atrophy involving six or more fibres out of ten along one edge of a fasciculus and not exclusive to type IIb fibres. Focal infarction may also occur. Regenerating fibres may surround necrotic fibres in basophilic cuffs, a feature rarely seen in the muscular dystrophies. In DM, the inflammation is usually in the perimysium, centered on the vessels and less often in the endomysium (Figure 1). Vasculitis may occur. B lymphocytes are as common as T lymphocytes around vessels and much less common within the fascicles. The T cell CD4/CD8 ratio is highest in perivascular and lowest in endomysial sites. There is upregulation of MHC class 1 antigens on the vascular endothelial cells (Figure 1). Ultrastructural examination shows tubuloreticular inclusions in the endoplasmic reticulum of membranous whorls (arrow) (G). Abnormal filamentous inclusions 12-18 nanometres in diameter are seen in the nucleus and cytoplasm (H). In polymyositis, fibre necrosis (double arrows) and endomysial inflammation is characteristic (single arrow) (I).

In IBM, scattered fibres contain single or multiple vacuoles termed ‘rimmed vacuoles’ characterised by small central or peripheral basophilic granules (Figure 1). Such vacuoles may contain round or oval eosinophilic and congophilic masses. The vacuoles may show discrete granular acid phosphatase activity. Ragged red fibres in excess of those expected for age may be seen. Several proteins, including Aβ, APP, ubiquitin, phosphorylated tau, α-synuclein, prion protein, presenilin-1, apolipoprotein E and survival motor neuron protein, have been shown to be associated with the vacuoles. Ultrastructural examination demonstrates that the basophilic granules in the vacuoles correspond to membranous whorls (arrow) (G).

Differential diagnosis

There are several potential pitfalls in biopsy interpretation which may lead to misdiagnosis. Demonstration of primary inflammation i.e. the CD8/MHC 1 complex is essential, as it is important in the pathogenesis of PM and IBM. MHC class 1 upregulation may be seen even in the absence of inflammation and should be routinely sought. Inflammatory changes may be associ-
ated with muscular dystrophies, including Duchenne and Becker muscular dystrophy, fascioscapulohumeral dystrophy, limb girdle muscle dystrophy type 2B and congenital muscular dystrophy with primary merosin deficiency. Appropriate immunohistochemical staining should be performed to assess reduced sarcosomal expression of proteins associated with muscular dystrophies. Inflammation may also be associated with toxic, necrotising and metabolic myopathies. Paraffin embedded muscle tissue is not suitable for the diagnosis of IBM as rimmed vacuoles are indiscernible. In some cases, inflammation may be patchy, resulting in sampling problems and repeat biopsy from a different site may be considered to confirm the diagnosis. Rimmed vacuoles may also be seen in a number of conditions including myofibrillar myopathies and oculopharyngeal muscular dystrophy and these must be considered in the differential diagnosis of IBM.

**Immunopathogenesis**

The specific target antigens initiating self-sensitisation in the IIMs remain unknown. In DM, the primary antigenic target is thought to be the endothelium of the endomysial capillaries. The predominant lymphocytes are B cells and CD4 T cells, consistent with a humoral immune response. Activation of complement leads to formation and deposition of the membrane attack complex C5b-9 on the endothelial cells. This results in lysis, intravascular thrombosis and capillary necrosis. Depletion of the capillary bed causes ischaemia, muscle necrosis and microinfarcts, endosarcosomal hyperperfusion and finally perifascicular atrophy. Cytokines and chemokines related to complement activation are released, upregulating adhesion molecules (VCAM-1, ICAM-1) on the endothelial cells. These in turn facilitate binding of T cells and macrophages via integrins and their egress into the perimysial and endomysial spaces.

In PM and IBM, CD8 T cells invade the MHC I expressing muscle fibres. There is evidence for clonal expansion of the autoimmune T cells being driven by specific antigens. The transmigration of activated T cells and adhesion to the muscle fibre is facilitated by cytokines (IL-1β and TNF-α), chemokines, adhesion molecules and metalloproteinases. Dendritic cells have been identified in the endomysial infiltrates of PM (and DM), although their role in antigen presentation remains unclear. Recent work on the pathogenesis of sporadic IBM suggests that abnormal accumulations of APP and Aβ, associated with the ageing cellular muscle fibre environment are key pathogenic events. Abnormalities of the APP processing machinery may occur and there may be preferential accumulation of the more toxic Aβ42 in IBM muscle fibres. Endoplasmic reticulum stress, in the form of upregulation of chaperone proteins, suggests that unfolded/misfolded proteins may participate in the pathogenic cascade. Recent studies have demonstrated strong Aβ-reactive and HLA-restricted T-cell responses against the immunogenic Aβ42 peptide in the elderly. It remains unclear whether Aβ can also serve as antigen, processed by the MHC class 1 expressing muscle fibres in sporadic IBM, leading to antigen-specific T cell activation.

**Treatment**

Current immunosuppressive therapies in PM and DM include high dose corticosteroids, azathioprine, intravenous immunoglobulins and cyclophosphamide. IBM does not respond well to treatment. The differential diagnosis is potentially large and muscle biopsies may be required in the elderly. Several studies have shown that Aβ deposition in PM and IBM is associated with Aβ deposits, and the tauopathies with tau deposits. These studies suggest that Aβ and tau deposition may be markers of a more generalized neurodegenerative process.

**Conclusion**

The IIMs are an important group of potentially treatable autoimmune diseases. IBM has a progressive course leading to severe disability and does not respond well to treatment. The differential diagnosis is potentially large and muscle biopsy is a crucial diagnostic test recommended before commencing treatment. Demonstration of primary inflammation (CD8/MHC 1 complex) is important and is central to the pathogenesis of PM and IBM. Neither the inflammatory changes nor rimmed vacuoles in IBM are entirely specific. Detailed histochemical and immunohistochemical studies, supplemented by biochemical and electron microscopic investigations will help to exclude other diseases that may mimic IIMs. These include the muscular dystrophies, metabolic myopathies including mitochondrial myopathy, toxic and uterine myopathies. Biopsies without well defined morphological abnormalities present the greatest difficulties and a close clinicopathological correlation is essential to reach a correct diagnosis.

**References**