

## Idiopathic inflammatory myopathies excluding inclusion body myositis

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The idiopathic inflammatory myopathies (IIMs), known collectively as myositis, constitute a large spectrum of clinical phenotypes. The classical clinical manifestation of IIMs, such as muscle weakness, relate to chronic inflammation in skeletal muscle. This inflammation also frequently affects other organs, including the skin, joints, lungs, gastrointestinal tract and heart, indicating the systemic nature of this disease. On the basis of muscle symptoms, skin rash, serological data and histopathological features, different subgroups have been identified in IIM including (a/hypomyopathic) dermatomyositis (DM), polymyositis (PM), immune mediated necrotizing myopathies (IMNM), non-specific or overlap myositis (NSM/OM), anti-synthetase syndrome (ASS), and inclusion body myositis (IBM)(Dalakas, 2015). DM, PM, IMNM, NSM/OM and ASS have a subacute onset and are treatable, whereas IBM is treatment-resistant. IBM will be the subject of another lecture.

Since first line therapy in the treatable IIM subtypes consists of long-duration high-dosage corticosteroids an accurate diagnosis is instrumental.

Except for patients with characteristic DM skin abnormalities, or those with a myositis in association with an obvious connective tissue disease, a muscle biopsy is necessary to confirm the diagnosis. There is much debate going on as regards the need for a muscle biopsy if myositis specific autoantibodies are found.

### *Selection of muscle biopsy*

Muscle biopsies should be taken from symptomatic muscles, either the quadriceps femoris or the deltoid. However, in 10-20% of cases muscle biopsy findings are inconclusive, due to sampling error caused by the scattered distribution of cellular infiltrates, even if a clinically affected muscle is biopsied. It is important to avoid muscle that has undergone recent EMG assessment. Muscle imaging may help select the most suitable biopsy site. In myositis, muscle MRI can demonstrate hyperintensity (muscle oedema) on STIR (short tau inversion recovery) and on fat-suppressed T2-weighted sequences (fig. 1), even in clinically asymptomatic muscles (Van de Vlekkert et al. 2015).

It may be useful to obtain an *en bloc biopsy*, i.e., encompassing skin, fascia and the subcutaneous tissue since the inflammatory infiltrates can also or predominantly be present in the skin, fascia or subcutaneous fat. A word of caution regarding the site of the skin biopsy, as skin changes such as erythema, are not necessarily associated with inflammation in the underlying muscles.

MRI may also be helpful to show inflammation of skin, fascia or subcutaneous tissue (Van de Vlekkert

et al. 2015)(fig. 1).

#### *Clinical data, lab studies and histology in IIM subtypes*

##### **Dermatomyositis**

DM is observed in adults and children. In this lecture only adult DM will be addressed. Evidence is accumulating that DM is a heterogeneous disease in itself, with various subtypes being distinguishable by characteristic clinical features and the presence of myositis specific antibodies (MSAs). Pathognomonic skin features (heliotrope rash, Gottron papules or sign), predominantly proximal muscle weakness and dysphagia, and anti-Mi-2 antibodies are found in classical DM, severe skin ulcers, little or no muscle weakness and interstitial lung disease (ILD) are associated with anti-MDA5 (Allenbach et al. 2016), cancer is often found in DM associated with anti-TIF1-gamma and NXP2 antibodies (20-30%). There is an increased risk of cancer up until three years after onset of DM. Creatine kinase activity in the serum (sCK) is varied, ranging from normal to 10 times the upper limit of normal.

Muscle biopsy typically demonstrates inflammatory infiltrates, mainly CD4+ T cells, macrophages, plasmacytoid dendritic cells (Greenberg 2007), CD20+ B cells, and rarely CD138 plasma cells, which are confined to the perimysium, often around blood vessels (Arahata and Engel 1984), perifascicular muscle fibre atrophy (Fig. 2)(Gitiaux et al. 2013), and scattered necrotic and regenerating muscle fibres. Major histocompatibility complex type I (MHC I) is upregulated in perifascicular muscle fibres. The earliest demonstrable histological abnormality in DM is deposition of the C5b-9 complement membrane attack complex (MAC) on small blood vessels (Emslie-Smith and Engel 1990). MAC precedes inflammation and other structural abnormalities on light microscopy, in particular in the perifascicular region which is considered to be specific for DM. Perifascicular atrophy is not found in amyopathic DM and is present in ~40% of adult patients with DM (Gitiaux et al. 2013; Uruha et al. 2017). Perifascicular atrophy is an end result of protracted local injury and incomplete repair (Lahoria et al. 2016). Myxovirus resistance A (MxA) expression in the myofiber cytoplasm has a much better sensitivity for the diagnosis of dermatomyositis (71%) compared to perifascicular atrophy and MAC deposition (35%)(Uruha et al. 2017).

A characteristic finding early in DM is the presence of tubuloreticular inclusions in endothelial cells, often preceding inflammatory cell infiltrates. These inclusions are related to the endoplasmic reticulum or to the outer nuclear membrane of the endothelial cell (De Visser et al. 1989) and are considered downstream markers of type 1 interferon signaling (Lahoria 2016).

##### **Non-specific or overlap myositis**

Non-specific or overlap myositis is defined as myositis occurring in association with a connective tissue disease (scleroderma, MCTD, Sjögren syndrome, rheumatoid arthritis) in approximately 20-30% of cases (Van der Meulen et al. 2003; Van de Vlekkert et al. 2014). Proximal muscle weakness with or without dysphagia is present. There are no skin abnormalities.

sCK is elevated ranging from two to ten times the upper limit of normal. Myositis associated antibodies including anti-Jo1, anti-Ro/SSA, anti-PM/Scl, anti-Ku and anti-U1RNP rather than MSAs are found in 40-70% (Vlekkert et al. 2016).

The histopathological picture may resemble that of DM, with perivascular cell infiltrates at perimysial sites, albeit predominantly composed of macrophages. Tubuloreticular inclusions in endothelial cells can be found in a proportion of cases of non-specific myositis associated with a connective tissue disorder (Bronner et al. 2008).

### **Antisynthetase syndrome**

The full-blown clinical picture is composed of myositis, arthropathy, interstitial lung disease (ILD), mechanic hands, fever and Raynaud phenomenon. However, there are patients who present with ILD and later develop myositis. Mechanic hands is observed in ~30%. Of the aminoacyl transfer RNA synthetase (ARS) antibodies anti-Jo1 is found in 30% of the cases (detected on a myositis line blot) followed by anti-PL7 and anti-OJ (the latter detected by RNA-immunoprecipitation and less accurate on a line blot).

Pathology in the perimysium and neighbouring muscle fibres is the hallmark of the histopathological picture of the anti-synthetase syndrome (ASS) (Mozaffar and Pestronk 2000). The most salient feature is the presence of necrotic and regenerating fibres which are strongly clustered in perifascicular regions (Fig. 3). Major histocompatibility complex (MHC) class I staining is diffusely positive, but particularly in the perifascicular area. Cellular infiltrates are mainly located in the perimysium and/or around vessels, often extending into the endomysium sometimes invading non-necrotic fibres. Inflammation is associated with perimysial fragmentation, highlighted by alkaline phosphatase staining. CD68+ macrophages are abundant (fig. 4) and in addition T cells (CD4+ cells and CD8+ cells), and to a lesser extent CD20+ B cells are observed (Mescam-Mancini et al. 2015).

### **Immune mediated necrotising myopathy**

Immune-mediated necrotizing myopathy (IMNM) is a relatively new entity within the spectrum of IIMs. IMNM mainly affects adults, but can also occur in children, sometimes mimicking a muscular dystrophy. The main clinical feature of IMNM is progressive - and often severe - limb-girdle muscle weakness. Dysphagia is described in 27-68%, weakness of the neck and back muscles in 36-71% and respiratory muscle weakness in 0-26% (Pinal-Fernandez et al. 2017; Suzuki et al. 2015; Watanabe et

al. 2016). IMNM may be associated with connective tissue diseases, with cancer (Allenbach et al. 2016) and rarely (10%) with ILD.

sCK may be as high as 500 times ULN (median 50 times ULN).

Identification of two myositis-specific auto-antibodies (MSAs), e.g., anti-3-Hydroxy-3-MethylGlutaryl-Coenzyme A Reductase (HMGCR) and anti-Signal Recognition Particle (SRP) auto-antibodies allowed for a serological classification (Mammen et al. 2011). About half of the patients with anti-HMGCR antibodies has been exposed to statins. One-third of IMNM patients do not have these MSAs and are called “seronegative” IMNM. Treatment outcomes vary and a majority of patients suffer from moderate to severe disability despite intensive multimodality treatments (Allenbach et al. 2014; Allenbach et al. 2017; Mammen et al. 2011; Pinal-Fernandez et al. 2017; Suzuki et al. 2015; Watanabe et al. 2016).

IMNM is characterized by the presence of necrotic muscle fibres with a scattered distribution as the predominant abnormal histological feature, distributed across the biopsy specimen (Fig. 5). There is macrophage predominant paucilymphocyte infiltration and sometimes prominent endomysial fibrosis (Stenzel et al. 2012).

### **Polymyositis – separate entity or IBM phenotype?**

As in IBM, in classical PM, mononuclear cells are mostly located in the endomysium and consist of predominantly CD8+ T lymphocytes, plasma cells, myeloid dendritic cells, and macrophages. The lymphocytes surround and may also invade non-necrotic muscle fibres that express MHC I on the sarcolemma. Thus, PM appears to be the result of a MHC I-restricted cytotoxic T-cell response against an (auto)antigen expressed by muscle fibres (Dalakas 2015).

Currently, there is much debate on the existence of PM (Van der Meulen et al. 2003; Vilela et al. 2015). Histopathologically defined PM shows a picture consistent with IBM, except for the absence of rimmed vacuoles in PM. If such a histopathological picture is found caution is required, and an active search made for clinical features pointing to a diagnosis of IBM, including asymmetry, weakness of distal muscles (deep finger flexors, anterior tibial muscles).

### *Therapy and outcome*

Currently all IIM subtypes are treated with high dosages of corticosteroids (prednisone or dexamethasone) as first line treatment. If there is severe muscle weakness methylprednisolone can be intravenously administered instead of oral steroids. If steroids do not suffice azathioprine or methotrexate or other second line drugs may be added. However, the effectivity of this medication has never been proven in RCTs. In IMNM intravenous immunoglobulin or rituximab is administered at a relatively early stage when steroids are not sufficiently effective after four weeks of treatment.

There is growing evidence to support the safety and efficacy of exercise in IIM patients. RCTs including adult patients with polymyositis and dermatomyositis and additional open studies have demonstrated reduced impairment and activity limitation as well as improved quality of life. In addition, recent studies have shown reduced disease activity assessed by consensus disease activity measures. These data suggest that intensive aerobic exercise and resistance training could reduce disease activity and inflammation (Alexanderson et al. 2016).

Myositis is a treatable disease, but most patients develop a polyphasic or chronic continuous disease course (~70%) and need maintenance treatment as is also often the case in other immune-mediated disorders such as myasthenia gravis. Over half of SRP-positive patients are refractory to various immunotherapy regimens (Suzuki et al. 2016). In a cohort of 62 IIM patients who were followed for approximately three years disability scores were found to improve in the first 18 months and subsequently stabilized. At follow-up, 68 % still perceived disabilities and reduced quality of life (Van de Vlekkert et al. 2014).

Thus, there is an urgent need for much better therapy for patients with IIM.

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