Idiopathic inflammatory myopathies (iims)

1. 1 Introduction to IIMs

Idiopathic inflammatory myopathies (IIMs) are a group of rheumatic disorders affecting skeletal muscle, they are thought to be auto immune in origin (Rothwell *et al.* , 2013), but as their name implies the actual cause remains something of an enigma. The phenotype of IMMs is generally characterised by progressive symmetrical proximal muscle weakness and rapid fatigue, MHC class 1 expression in muscle fibres (van der Pas *et al.* , 2004), increased circulating muscle enzymes (Creatine kinase, lactate dehydrogenase)(Cox *et al.* , 2010), and the invasion of inflammatory infiltrates such as immune cells and cytokines (Lundberg *et al.* , 1997; Grundtman *et al.* , 2007). They are heterogeneous in their clinical presentation with patients displaying differing histopathological features, and exhibiting varying disease durations and treatment responses; this is probably associated with the numerous genetic and environmentally implicated factors that have been recently discovered (Rothwell *et al.* , 2013). Interestingly, overt muscle atrophy is not a typical feature of IMM as it is in most diseases associated with muscle fatigue.

Inflammatory infiltrate presence in muscle fibres is indicative of cytotoxicity (Lundberg *et al.* , 1997). However, it is often observed that the extent of infiltrate presence in the muscle fibre does not often correlate with the degree of muscle dysfunction (Grundtman *et al.* , 2010), implying that impaired muscle performance is the result of something other than muscle cell damage induced by inflammatory cells and their products; and the continued progression of pathology in the absence of infiltrates suggests that the muscle itself could be contributing. Furthermore, it has been found

that weakness can in-fact precede infiltrate presence, and in immune-suppressed individuals weakness can persist (Lundberg & Chung, 2000). Muscle weakness is usually initiated in the large muscles around the hips and shoulders, but often spreads to more distal areas resulting in quadriparesis (weakness in all four limbs) that can be severely debilitating. The impact of this can cause the patient difficulty in carrying out even simple everyday tasks such as climbing stairs and can be particularly dangerous in older patients who often have related morbidities. As the disease progresses, eventually the patient's fine motor skills can be impeded: distal muscle action is required for these movements and weakness in these regions can have affect fine motor skills (Dalakas, 1991). Dysphagia (difficulty swallowing) is also common in severe cases and can cause fatal choking.

IMMs clearly have an adverse impact on the patient's quality of life, and a deeper understanding into the disease is essential for this to be improved. However, some patients are only mildly affected; this heterogeneity makes it difficult to establish the definitive cause of myositis, and treatment is therefore limited.

IMMs can be subdivided into three main discrete histological categories: Polymyositis, Dermatomyositis, and Inclusion Body Myositis.

1. 2 Dermatomyositis (DM)

DM is a microangiopathy that affects both the skin and muscle tissue, and is caused by the lysis of endomysial capillaries and muscle ischemia (Dalakas & Hohlfeld, 2003). It was Hohlfeld that described the criteria for diagnosing IMMs; a diagnosis can be made subsequent to three laboratory experiments:

serum muscle enzyme concentrations, electromyography, and muscle biopsy (Dalakas & Hohlfeld, 2003), and in some cases a skin biopsy may be useful in diagnosing DM. Creatine Kinase (CK) elevation is the main indicator of DM, and is usually correlative to disease severity. It is common for skeletal muscle CK concentration to increase fifty-fold in patients with active DM, but in some patients levels remain basal (Dalakas & Hohlfeld, 2003). The muscle biopsy is critical for an accurate diagnosis and would generally show perifascicular atrophy caused by phagocytosis and necrosis of the muscle fasciculus; this is diagnostic of DM even in the absence of inflammation. CD4 positive T-cells are usually detected in the dermis at sites of perivascular inflammation, and capillary density is dramatically reduced with vessel perforation.

DM was unsurprisingly the first to be reported in 1875 by Potain (Potain, 1875) (Oddis & Medsger Jr, 1995), probably due to its extramuscular manifestation of heliotrope (upper eyelids), and erythematous (face, neck, back, shoulders) rashes that commonly precede muscular weakness (Dalakas & Hohlfeld, 2003). The extensor joint surfaces of DM sufferers are commonly covered in Gottrons papules, along with dilated capillary loops at the base of the finger nail with thickened cuticles (Dalakas & Hohlfeld, 2003). The outward appearance of DM often leads to a false diagnosis of systemic lupus erythematosus as muscle weakness is not always evident in DM patients; however, the two diseases differ in that only the latter involves a phalangeal rash. DM has been shown to be the most common form of juvenile myositis, though there have been reported rare incidences of polymyositis (Sato *et al.* , 2000).

If treated early on, DM has been shown to respond to immunotherapeutic agents; however, the first line of treatment is usually corticosteroids such as high-dose oral Prednisone. Patients usually show some degree of response to steroid treatment alone, but they are usually administered in conjunction with other immune targeted treatments (Aggarwal & Oddis, 2012).

1. 2 Polymyositis (PM)

In 1887 Unverricht reported the first case of PM (Unverricht, 1887), which presents without the classical rash associated with DM. It is the least common form of myositis and onset is almost universally after 18 years of age, though as previously mentioned it has been reported in the juvenile form (Sato *et al.* , 2000). Epidemiology of PM is difficult to quantify due to it being a rare form of a rare disease that was for many years indistinguishable from Inclusion Body Myositis. PM develops slowly over months or years, and identifying the exact, or even approximate, time of onset is difficult due to the progressive nature and lack of the characteristic rash associated with DM. Muscle weakness progresses in much the same way as DM and is equally as debilitating (Dalakas & Hohlfeld, 2003).

Diagnosing PM generally involves the exclusion of other similar myopathies using the three diagnostic laboratory experiments described earlier. In PM, unlike DM, CK concentration is always elevated significantly above the basal level. CD8-positive T-cells are found to be invading healthy muscle fibres expressing MHC class I antigens forming a CD8/MHC-1 complex (Dalakas & Hohlfeld, 2003). There has long been evidence to suggest that PM could be

induced by viral infiltration, possibly via retro-viral infection (Dalakas *et al.* , 1986).

The treatment approaches for PM are the same as DM, and in about 70% of patients intravenous immunoglobulin appears to be a promising treatment.

1. 3 Inclusion Body Myositis (IBM)

IBM was not universally accepted as a separate classification to DM and PM until 1978 (CARPENTER *et al.* , 1978), but it has since been found to be the most common acquired IMM in the elderly, and in men over the age of fifty (Dalakas & Hohlfeld, 2003). There are two types, sporadic- and hereditary-IBM, the two are histologically and ultrastructurally similar, but hIBM lacks inflammation. IBM was pathologically characterised by Yunis and Samaha, who coined the term in 1971 (Yunis & Samaha, 1971); they noted in patients the presence of vacuoles containing cytoplasmic degradation products with fibrillary nuclear and cytoplasmic inclusions that distinguished IBM from PM, something it is often misdiagnosed as. Insoluble amyloid protein deposits are also found in the muscle tissue of IBM patients, along with the invasion of CD8/MHC-1 complexes that are also associated with PM, and perivascular and endomisial inflammatory infiltrates (Grau & Selva-O'Callaghan, 2008). CK levels are usually, but not always, elevated slightly.

The vacuoles associated with IBM are indicative of muscle atrophy, something that is not generally seen in DM or PM. The process is gradual, occurring slowly over years similarly to many muscular dystrophies. In PM patients that do not respond to therapy, a diagnosis of IBM is now generally considered. Most IBM patients do not show a marked response to anti-

inflammatory or immunosuppressant therapy; a few, probably those with an early diagnosis, show a limited response to corticosteroids, and cytotoxic drugs, but this is not always sustained. Exercise therapy is often suggested to stabilize muscle strength and function, and is frequently advised (Grau & Selva-O'Callaghan, 2008).

1. 4 Epidemiology

Onset of myositis is most common in adults and is generally sporadic, though it has been postulated that there could be some underlying genetic predisposition that could attribute to myositic presentation in some individuals (Cox *et al.* , 2010; Rothwell *et al.* , 2013). Juvenile myositis is less common than the adult form, with dermatomyositis being most prevalent (Dalakas & Hohlfeld, 2003); it's incidence creates discrete age brackets in which IIMs occur. IIMs are regarded as rare, and though there have been numerous attempted epidemiological studies they generally have a low sample size, and it is therefore difficult to determine accurate statistics; also, most statistics are no longer accurate as the old classification of IMMs (Bohan and Peter) could not distinguish between Polymyositis and Inclusion Body Myositis. IMMs have been shown to be most prevalent in women, with DM being the most common diagnosis (Dalakas & Hohlfeld, 2003).

1. 4 High Mobility Group-box 1 Protein (HMGB1)

HMGB1 is a non-histone chromatin associated protein; under typical physiological conditions it is confined within the nucleus where it regulates an array of important transcriptional pathways by binding to and distorting sections of DNA, allowing for the assembly of multi-protein complexes

(Bianchi & Manfredi, 2004). In response to tissue damage, the normally nuclear protein translocates to the extracellular space and acts as an inflammatory cytokine. Excessive cytokine signalling by HMGB1 has been shown to be fatal in mice (Wang *et al.* , 1999).

However, it has been observed that in models of tissue regeneration HMGB1 acts as a chemotactic agent to recruit stem cells such as mesangioblasts in vitro, which indicates it has an in vivo role of favouring muscle regeneration by promoting vessel formation (Vezzoli *et al.* , 2011) (Sachdev *et al.* , 2013). It is therefore interesting that it’s implicated role in IMMs is pathological.

1. 5 HMGB1 in IIMs

When activated by inflammatory stimulants, HMGB1 is actively secreted from monocytes and macrophages via specialised organelles such as secretory lysosomes (Bianchi & Manfredi, 2004); HMGB1 is found to be significantly elevated in patients with IIMs (Grundtman *et al.* , 2010). This translocation is permitted by the hyperacetylation of lysines on HMGB1 (Bonaldi *et al.* , 2003) allowing it to be permanently dissociated from the chromatin, and become packaged in secretory lysosomes. In necrotic cells the cellular membranes lose their integrity and soluble proteins such as HMGB1 are allowed to leak out; this differs from apoptosis where the cell death is not signalled by this leak as HMGB1 remains tightly bound to the chromatin (Bianchi & Manfredi, 2004). Necrosis is thought to be the predominant route for cell death in IIMs (Schneider *et al.* , 1996); this allows for HMGB1 to be passively released from the cell.

HMGB1 exists in mutually exclusive redox forms that mediate specific inflammatory roles (Venereau *et al.* , 2012). Full reduction of Cysteines 23, 45, and 106 occurs initially, forming all-thiol-HMGB1; in this state it has a cytokine stimulating activity. It is thought that this is the form secreted by activated monocytes to help contribute to the inflammatory response. Later, a disulphide bond forms between C23 and 45 in the HMG-BoxA domain of HMGB1 whilst the Box B C106 remains unpaired and in the thiol state (Venereau *et al.* , 2012). The disulfide form possesses chemoattractant capabilities, causing the migration of leukocytes to the region of inflammation (Venereau *et al.* , 2012). Only the fully reduced form can recruit motile cells, making the cytokine stimulating and chemoattractant activities of HMGB1 also mutually exclusive.

Terminal oxidation of HMGB1 fully abrogates its bioactivity, but slight oxidation is required to convert all-thiol HMGB1 to disulphide-HMGB1; it is thought that infiltrating inflammatory cells cause the conversion by maintaining the extracellular oxidative environment as they are a well characterised source of reactive oxygen species (ROS).

HMGB1 is a ligand for the Toll-like Receptor 4 (TLR4), a mediator of the innate immune response; though it is found in both healthy individuals and myositis patients, it is proposed to be the receptor for which muscle dysfunction in IIMs is mediated (Zong *et al.* , 2013). The TLR4 plays an important role macrophages and monocytes where it is involved in pathogen recognition. Patient data from a recent study suggests that HMGB1 may induce MHC class 1 expression in patients with IIMs via activation of the TLR4: MHC class 1 and TLR4 have been found to be coexpressed in the

muscle fibres of patients with myositis but not healthy individuals (Zong *et al.* , 2013). Another receptor through which HMGB1 signals is the Receptor for Advanced Glycation Endproducts (RAGE); an in-vitro knock out study using intact single fibres demonstrated that HMGB1 acts via the TLR4 and not RAGE to induce muscle MHC class 1 expression and fatigue by decreasing the Sarcoplasmic Reticulum (SR) Ca2+ released by action potentials (Zong *et al.* , 2013). However, this may not necessarily be true in-vivo. Nevertheless, the HMGB1-TLR4-MHC 1 pathway seems to be an integral part of the pathogenesis of IMMs and could therefore be a potential therapeutic target. It has been shown that aerobic exercise (a common and beneficial intervention for IIM patients) reduces TLR4 mRNA in skeletal muscle of rats (Zanchi *et al.* , 2010), thus further suggesting that TLR4 plays a key role in IMMs.

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