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Inflammatory myopathies: update on diagnosis, pathogenesis and therapies, and COVID-19-related implications

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The inflammatory myopathies constitute a heterogeneous group of acquired myopathies that have in common the presence of endomysial inflammation. Based on steadily evolved clinical, histological and immunopathological features and some autoantibody associations, these disorders can now be classified in five characteristic subsets: Dermatomyositis (DM) Polymyositis (PM), Necrotizing Autoimmune Myositis (NAM), Anti-synthetase syndrome-overlap myositis (Anti-SS-OM), and Inclusion-Body-Myositis (IBM). Each inflammatory myopathy subset has distinct immunopathogenesis, prognosis and response to immunotherapies, necessitating the need to correctly identify each subtype from the outset to avoid disease mimics and proceed to early therapy initiation. The review presents the main clinicopathologic characteristics of each subset highlighting the importance of combining expertise in clinical neurological examination with muscle morphology and immunopathology to avoid erroneous diagnoses and therapeutic schemes. The main autoimmune markers related to autoreactive T cells, B cells, autoantibodies and cytokines are presented and the concomitant myodegenerative features seen in IBM muscles are pointed out. Most importantly, unsettled issues related to a role of autoantibodies and controversies with reference to possible triggering factors related to statins are clarified. The emerging effect SARS-CoV-2 as the cause of hyperCKemia and potentially NAM is addressed and practical guidelines on the best therapeutic approaches and concerns regarding immunotherapies during COVID-19 pandemic are summarized.

Key words: dermatomyositis, polymyositis, inflammatory myopathies, COVID-19

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Introduction

Inflammatory myopathies (IM) are a heterogeneous group of acquired myopathies that have in common the presence of inflammation in the muscle. Based on distinct clinical, histological, immunopathological and autoantibody features, they have evolved in five distinct subsets: Dermatomyositis (DM), Polymyositis (PM), Necrotizing Autoimmune Myositis (NAM), Anti-synthetase syndrome-overlap myositis (Anti-SS-OM), and Inclusion-Body-Myositis (IBM) [1-6]. Each subset has distinct clinical features, pathogenesis, response to therapies and different prognosis requiring careful clinicopathologic correlation with expertise in muscle histopathology for a correct diagnosis and distinction from disease mimics. The article describes the main clinicopathologic and immune features of all subtypes, highlights

how best to avoid erroneous diagnoses, and provides practical guidelines on therapeutic approaches.

Patients with all IM forms experience slow, subacute and rarely acute onset of difficulty performing tasks requiring the use of proximal muscles, such as climbing steps or getting up from a chair; patients with IBM however, may present first with weakness in the distal muscles of hands and feet and difficulties with buttoning, typing or raising toes and feet. Neck-extensor and pharyngeal muscles can be affected in all subsets resulting in difficulty holding up the head (head drop) and dysphagia. In advanced cases, respiratory muscles can be affected. Myalgia and muscle tenderness may also occur, most often in anti-SS-OM; if myalgia is prominent, a co-existent fasciitis should be considered. Extramuscular manifestations may occur in all IM, but rarely in IBM, and include arthralgia, Raynaud's phenomenon and pulmonary complications due to interstitial lung disease as seen in anti-SS-OM [1-6] or in amyopathic DM with anti-Melanoma Differentiation–Associated protein-5 [MDA-5] antibodies [1,7].

Clinical characteristics

Dermatomyositis (DM)

DM, seen in both children and adults, presents with characteristic skin manifestations accompanying or preceding muscle weakness. Periorbital heliotrope (blue-purple) rash with edema, erythematous rash on face, knees, elbows, malleoli, neck, anterior chest (in V-sign), back and shoulders (in shawl sign), and knuckles with a violaceous eruption (Gottron's rash) that evolves into a scaling discoloration, are typical skin lesions [1-8]. Dilated capillary loops at the base of the fingernails, irregular and thickened cuticles, and cracked palmar fingertips ("mechanic's hands") are also characteristic [1-4]. Subcutaneous calcifications, sometimes extruding to the surface, were common in our practice 20-30 years ago especially in children, as highlighted [8], but they are rarely seen today due to early initiation of effective immunotherapies. When DM is clinically limited to the skin (amyopathic dermatomyositis), the patients seem to have normal strength, but their muscle is always subclinically involved; based on our experience with a number of such patients we have biopsied, their muscle shows the typical features of DM described below but to a lesser degree [9]. In children, an early symptom is "misery," defined as an irritable child with red-flush on face, fatigue and reluctance to socialize [1-4]. Dermatomyositis may overlap with systemic sclerosis and mixed connective tissue disease and requires distinction from the anti-SS-OM subset. In adults with DM there is a malignancy risk in up to 15% of patients, especially in the first 3-5 years from the disease onset [1,8]. Common cancers are ovarian, breast, colon, melanoma, nasopharynx (in Asians) and non-Hodgkin lymphoma, necessitating a thorough annual work-up the first 3 years [10].

Polymyositis (PM)

PM is a very rare entity. In our experience most patients referred for PM have another disease most often IBM, NAM, or an inflammatory dystrophy [1-3]. Polymyositis does exist but remains a diagnosis of exclusion. It is best defined as a subacute proximal myopathy in adults who do not have rash, family history of neuromuscular disease, exposure to myotoxic drugs (d-penicillamine, zidovudine), involvement of facial and extraocular muscles, endocrinopathy, or the clinical phenotype of IBM [1-3].

Necrotizing Autoimmune Myositis (NAM)

NAM, also referred by some as Immune-mediated necrotizing myopathty (IMNM), has now evolved as the most common IM subtype [1]. It starts either acutely reaching its peak over days or weeks, or subacutely progressing steadily causing severe weakness and very high creatine kinase (CK) levels in the thousands [1]. NAM may also occur after viral infections and in association with cancer or immune check point inhibitors as discussed later. Unfortunately, very often NAM is erroneously attributed to statins or over-diagnosed as a "statin-myopathy" in patients on chronic statin administration [11], even though there is no convincing evidence as explained later. Acute rhabdomyolysis, like seen in NAM, can very rarely coincide with statin initiation and may be the causative factor in some cases of acute-onset NAM but there is no convincing evidence that statins play a triggering role in patients who develop a subacute NAM, *while taking statins for years* and their myopathy continues to worsen even after statin withdrawal [1,11,12]. Most NAM patients have antibodies against signal recognition particle (SRP) or 3hydroxy3-methylglutaryl-coenzyme A reductase (HMG-CR) [1,11,14] as discussed later.

Anti-synthetase syndrome-Overlap Myositis (Anti-SS-OM)

Anti-SS-OM, often presents with systemic sclerosis-like lesions, mild-to-moderate proximal muscle weakness, arthritis in the form of subluxation of the interphalangeal joints, "mechanic's hands", Raynaud phenomenon, and interstitial lung disease [1]. The syndrome is highlighted by the presence of anti-synthetase antibodies, primarily anti-Jo-1, hence the naming of *anti-Jo-1 syndrome,* and distinct histology with necrotizing features in the perimysium and perifascicular muscle fibers [1,11,16].

Inclusion Body Myositis (IBM)

This is the most common and disabling inflammatory myopathy above the age of 50 [1-5,17,18]. It starts

insidiously, over years, at times asymmetrically, and progresses steadily simulating a late-life muscular dystrophy or slowly progressive motor neuron disease [1-3]. Although IBM is commonly suspected when a patient with presumed PM did not respond to therapy [1-3], early involvement of distal muscles, especially foot extensors and finger flexors, atrophy of the forearms and quadriceps muscles, frequent falls due to quadriceps muscle weakness causing buckling of the knees, and mild facial muscle weakness, are clues to early clinical diagnosis [1-5,17-21]. Axial muscles may be affected resulting in camptocormia or head drop. Dysphagia occurs in more than 50% of the patients. [1-5,17-21] IBM is a progressive disease leading to disability.

Diagnosis and diagnostic work-up

The diagnosis of IM is based on the combination of clinical history including the pattern of muscle involvement and tempo of disease progression (as described above), combined with determination of serum muscle enzymes, muscle biopsy findings and at times auto-antibodies. Ancillary information is provided by electromyography, which can be useful to exclude neurogenic conditions or assess disease activity. Muscle MRI with contrast can reveal edema and inflammation in muscle and fascia and is mainly useful to define and assess the distribution of atrophic muscles[1]. The usefulness of muscle MRI has been excessively overestimated because the findings are not diagnostic for an IM and, contrary to suggestions that it can help selecting the specific muscle to biopsy, it does not provide more than a careful neurological examination because the surgeon can still obtain tissue from a very atrophic muscle fascicle since the biopsy is not MRI-or CT-guided and within the seemingly viable muscle tissue there are long atrophic fascicles (Dalakas unpublished observations).

Serum muscle enzymes

Creatine Kinase is elevated in all subtypes with active disease but can be normal when the disease has become chronic. Very high levels point to NAM, while normal levels from the outset can be seen in DM and anti-SS-OM reflecting predominant pathology in the interstitial tissues. Aldolase may be also elevated especially if the fascia is involved [1,24-26].

Muscle biopsy findings

It shows features distinct for each subset and, although not always typical, remains the most reliable diagnostic tool when interpreted in the context of the clinical findings and processed in the clinician's expert laboratory that performs enzyme histochemistry and immunocytochemistry. Findings for each subtype are:

a) in dermatomyositis, there is inflammation predominantly perivascularly, in the interfascicular septae or at the periphery of the fascicles. The muscle fibers undergo necrosis and phagocytosis, often in a portion of a muscle fasciculus or the periphery of the fascicle, due to microinfarcts leading to hypoperfusion and perifascicular atrophy [1-5,25]. Perifascicular atrophy, characterized by layers of atrophic fibers at the periphery of the fascicles, often with perivascular infiltrates, is diagnostic of dermatomyositis even without skin manifestations [1-5, 24,25,26];
b) in anti-synthetase syndrome-Overlap Myositis the histology may overlap with that of DM but this entity predominantly affects the perimysium with necrotizing features of the perimysial and perifascicular areas along with actin myonuclear inclusions [1,16,17,25,26];
c) in polymyositis there is inflammation perivascularly and in multiple foci within the endomysium consisting predominantly of $CD8^+$ T cells invading healthy, non-necrotic, muscle fibers expressing MHC-I antigen (normal muscle fibers do not express MHC-I antigen) [1-5].
   The MHC/CD8 complex is useful to confirm the diagnosis and exclude disorders with non-immune inflammation, as seen in some muscular dystrophies [1-5,17,25];
d) in Inclusion Body Myositis (IBM), in addition to the same inflammatory pattern described for PM, there are chronic myopathic changes with increased connective tissue and fiber-size variability; autophagic vacuoles with bluish-red material "ragged-red" or cytochrome oxidase–negative fibers due to abnormal mitochondria; and congophilic amyloid deposits next to the vacuoles best visualized with crystal violet or fluorescent optics [1-5,17,18, 20,21]. In up to 30% of IBM patients with the typical clinical IBM- phenotype, the biopsy does not show vacuoles or amyloid deposits but only inflammation, leading to erroneous diagnosis of polymyositis [1,17]. Such patients have *clinical IBM* diagnosed on clinicopathologic correlations [1,17,27];
e) in *necrotizing autoimmune myositis* there are abundant necrotic fibers invaded or surrounded by macrophages. Lymphocytic infiltrates are sparse and MHC-I upregulation mostly in the necrotic fibers[1-5,17,25]. In a number of patients, the muscle biopsies show deposition of complement on blood vessels and, as expected, on necrotic fibers. Up to 65% of the patients have specific, albeit non-pathogenic, antibodies[1,12-14,17].

Autoantibodies

Directed against nuclear RNAs or cytoplasmic antigens, autoantibodies are detected in up to 75% of all IM patients depending on methodology [1]. Although their pathogenic role is unclear, some antibodies appear specific for distinct clinical phenotypes. They include:

a) anti-*aminoacyl-tRNA synthetases*, detected in 20-30% of the patients [1,11,28,29]. Among the eight different anti-synthetases, the antibodies directed against the histidyl-transfer RNA synthetase (anti-Jo-1), is the most common accounting for 75% of all anti-synthetases and defines the "anti-synthetase- syndrome" described above;
b) *necrotizing autoimmune myositis-specific antibodies*, against the translational transport protein SRP (Signal Recognition Particle) or against a 100-kd autoantigen identified as HMGCR (3hydroxy3-methylglutaryl-coenzyme A reductase). Because HMGCR is the pharmacological target of statins [1,11-14], these antibodies have been thought to be associated with a prior statin use. These antibodies however are more often seen in statin-naive patients, and they are detected in up to 65% of all NAM cases from any cause [1,13,17]. Most importantly, anti-HMGCR may be more often associated with malignancies rather than statins. They are disease markers and, contrary to some publications, they do not have a pathogenic role as explained below;
c) *dermatomyositis-associated antibodies* that include: i) Mi-2, highlighting the typical skin lesions; ii) melanoma differentiation–associated protein-5 (MDA-5) mostly connected with amyopathic dermatomyositis or interstitial lung disease [1,30]; and iii) transcriptional intermediary factor-1 (TIF-1) and nuclear matrix protein NXP-2, highly connected with cancer-associated adult DM [30]; and
d) *anti-cytosolic 5'-nucleotidase- 1A (cN1A*), detected in 33-51% of IBM patients [31]. These antibodies have no pathogenic significance, and they can be also seen in patients with other types of myositis or rheumatic diseases. Their presence in IBM highlights however the immune dysregulation and B-cell activation.

Triggering factors and associations

Malignancies

Two IM subtypes are associated with malignancies, DM and NAM. In DM with malignancy a common antibody is the one against transcriptional intermediary factor-1 (TIF-1), while in NAM antibodies against HMGCR, especially in patients above the age of 50, are most frequent. Among 349 patients with IM, 75 (21%) had cancer manifested usually within a year; among those patients, 48% had DM with anti-TIF-1 antibodies and the other half had NAM with HMGCR [13].

Immune check-point inhibitors (ICPI's)

An increasing number of patients with advanced malignancies treated with ICPI's can develop immune-related neurological complications including inflammatory myopathies [32,33]. The neurological events can evolve rapidly, necessitating the need for vigilance at all stages of treatments, even after completion, because early immunotherapeutic interventions with steroids and IVIg are effective. The main ICPIs currently on the market are directed against a) CTLA-4: *Ipilimumab*; b) PD-1: *Pembrolizumab and Nivolumab*; and *c)* PD-L1: *Atezollizumab, Avelumab, and Durvalumab.* The process by which ICPI's trigger autoimmunity has been discussed elsewhere [32]. Briefly, tumors, like other antigen presenting cells, express on their cell surface the inhibitory ligands PD-L1/PDL-2 and B7-1/B7-2 which are respectively engaged with PD-1 and CTLA-4 on T cells, downregulating T cell responses. These receptor/ligand interactions essentially act as an *off switch,* like "telling the T cells to leave the tumor cells alone" so T cells do not attack the tumor[3 2]. The ICPI's prevent the CTLA-4 or PD-1 from binding to their respective receptors CD80/86 and PDL-1 and, by doing so, inhibit the inherent "inhibitory" costimulatory interactions between T cells and tumor cells, resulting in positive signals. What ICPI's essentially do is turning the *switch back on* resulting in positive costimulation and strong cell activation, like taking the *brakes off* the immune system [32]. This blockade allows the T cells to kill tumor cells, but at the same time the resulting enhanced co-stimulation causes an uncontrolled T cell activation that disrupts immune tolerance resulting in immune-related events against muscle.

Among all the inflammatory myopathy subtypes, the most frequent autoimmune myopathies triggered by pembrolizumab, ipilimumab and nivolumab are DM and especially NAM. In some patients, NAM may co-exist with myasthenia gravis presenting with head drop, proximal muscle weakness, myalgia, dyspnea, ophthalmoparesis or bulbar weakness. Among 654 patients receiving ICPI's (pembrolizumab: 389; nivolumab: 264; both: 1), 5 on pembrolizumab had biopsy proven myopathies (2 NAM, 1 dermatomyositis, and 2 nonspecific myopathy) 33. Patients respond to steroids and IVIg especially if treated promptly.

Viruses, including SARS-CoV-2

Among potential triggers, except of the Immune checkpoint inhibitors discussed above, viruses have clearly the potential to break tolerance and trigger an im-

mune inflammatory myopathy. Although IM have been seen during or after a viral infection, attempts to amplify viruses from the muscles, including coxsackieviruses, influenza, paramyxoviruses, mumps, cytomegalovirus and Epstein-Barr virus, have failed [1-5]. The best studied viral connection until now has been with retroviruses. Patients infected with HIV or human-T-cell-lymphotropic virus-I develop polymyositis or inclusion-body myositis [1-3, 34-35] with retroviral antigens detected not within the muscle parenchyma but within some endomysial macrophages (Trojan-horse mode). The autoinvasive T cells are however clonally driven and some are retroviral-specific [35].

During the present COVID-19 pandemic**,** there is evidence that more than 10% of COVID-19-infected patients develop myopathic symptoms with myalgia, weakness and elevated CK sometimes at very high CK levels > 10,000 suggestive of Necrotizing Autoimmune Myositis (NAM) [36]. Although COVID-19-associated myositis has not yet been studied but only characterized as "skeletal muscle injury" or "rhabdomyolysis", two just published cases suggest an autoimmune COVID-19-triggered NAM as summarized [36]. One, an 88-year old man from New York presented with acute bilateral thigh weakness and inability to get up from the toilet, without fever or other systemic symptoms, and very high CK level (13,581 U/L) [36]. He was found COVID-19-positive, given hydroxychloroquine and a week later his painful weakness improved with CK reduction. The other, a 60-year-old man from Wuhan had a 6-day history of fever, cough and COVID-19-positive pneumonia with normal strength and CK; seven days later, although systemically had improved, his CRP doubled and developed painful muscle weakness with very high CK (11,842 U/L) [36]. He was given IVIg and his strength improved while became COVID-19-negative.

In a recent retrospective study, patients hospitalized for a flue also had elevated CK level as high as those seen in a large series of patients with COVID-19 [37] confirming the long-term notion that hyperCKemia can frequently occur in sick patients with an acute viral illness [1-3]. However, an acute onset of severe muscle weakness with increased inflammatory markers and very high CK levels in the thousands, as noted in the two cases above, is highly suggestive of an autoimmune inflammatory myopathy within the spectrum of NAM triggered by the virus, similar to what we first reported with HIV early in that epidemic [35,36]. Considering that very high CK level and painful muscle weakness were seen in 10% of COVID-19-positive patients [36], a potentially treatable autoimmune myopathy might have been likely overlooked. This notion however requires a great deal of caution because without muscle biopsy confirmation and antibody screening, the diagnosis of COVID-19-NAM remains still undocumented because myopathic symptoms in a severe systemic viral disease are multifactorial [37]. The need to study COVID-19 muscle invasion is therefore needed and will be highly interesting because ACE2, the SARS-CoV receptor, is reportedly expressed in skeletal muscle [summarized in [37]]. If this is confirmed, COVID-19 may represent the first virus directly capable of infecting muscle fibers. None of the viruses implicated as possible myositis triggers has been shown to directly infect the muscle fiber and our molecular studies have so far failed to detect any of them [38]; instead, viruses induce an immune T cell-mediated with clonal expansion of viral-specific T cells, or macrophage-mediated, muscle fiber autoinvasion with abundant pro-inflammatory cytokines [1-3, 35,36].

Statin exposure

A very small number of patients early on statin initiation may experience transient myalgia, and some others transient CK elevation but no muscle weakness. In some patients, myalgia persists demonstrating statin intolerance. Very rarely, patients may develop rhabdomyolysis soon after statin initiation. The implication however that *chronic* statin administration can, all of a sudden, trigger " statin-myopathy" in the form of NAM [11,14] with antibodies against HMGCR, a ubiquitous and non-muscle-specific antigen within the endoplasmic reticulum, has never been substantiated. Statins can upregulate HMGCR in cultured cells in vitro, and HMGCR is the target of action of statins, but studies from many centers throughout the world have consistently shown that anti-HMGCR autoantibodies are more often seen in statin-naïve NAM patients and more often connected with cancer [13,39,40]. Since NAM is now the commonest inflammatory myopathy and more than 25% of Americans above 40 years take statins, the association between statins and NAM is likely a chance phenomenon [1,17,41,42]. Some authors correctly proposed that the term "statin myopathy" should not be used [40] because only a minority of NAM patients had statin exposure and, even in those patients, NAM appears many years after statin initiation making a causative role dubious if not impossible.

Immunopathogenesis

Although the causes of inflammatory myopathies are unknown, an autoimmune pathogenesis is strongly implicated, and seems to be specific for each subset.

Dermatomyositis

In DM, early activation of complement C5b-9 membranolytic-attack-complex is deposited on the endothelial cells [1-5,43], leading to capillary necrosis, reduction of endo-

mysial capillaries, ischemia, and muscle-fiber destruction resembling microinfarcts [1-5]; the remaining capillaries have dilated lumens to compensate for the ischemia [1-5]. The residual perifascicular atrophy reflects the endofascicular hypoperfusion, which is most prominent at the periphery of the fascicles. The membrane attack complex activation is triggered by binding of C1q to endothelial cells and releases proinflammatory cytokines, upregulates the adhesion molecules on endothelial cells, and facilitates the migration of activated lymphocytes including B cells, $CD4^+$T cells and plasmacytoid-dendritic cells to perimysial and endomysial spaces. Innate immunity also plays a role based on increased expression of type-I interferon-inducible proteins in the perifascicular regions [44]; this effect appears secondary to ischemic damage which is probably sensed by the retinoic acid-inducible gene-1 signaling leading to auto-amplification of local inflammation by activating β-interferon and MHC-1 [45].

Necrotizing autoimmune myositis and the misconception of statin association or pathogenicity of antibody markers

Within the necrotic fibers of NAM, there are macrophages, MHC-I expression and deposition of complement; these findings have been loosely interpreted to suggest that in NAM there is complement- mediated cytotoxicity and the recruitment of macrophages invading the muscle fibers represent an antibody-dependent cell-mediated cytotoxicity (ADCC) process [11,14,46]. There is no convincing evidence however supporting a pathogenic role of these antibodies in causing or triggering muscle fiber necrosis via an ADCC mechanism [41,42]. Both, SRP and HMGCR antibodies, are against ubiquitous and non-muscle-specific antigens firmly localized in the endoplasmic reticulum and there is no explanation how antibodies against such cytoplasmic targets can selectively cause muscle fiber cell necrosis, as discussed [41]. Further, MHC-1-expression and C5b-9 complement deposits are *always* observed in necrotic and regenerating fibers from any cause, such as commonly in muscular dystrophies [47,48], and lack specificity for NAM. Classic work of AG Engel et al dictates that *all* necrotic fibers in non-immune myopathies, such as muscular dystrophies, unambiguously activate complement which in turn stimulates cellular infiltrates and macrophages [47,48]. Further, claims that these antibodies can cause muscle fiber atrophy or affect regeneration in vitro[49] are irrelevant to the cause of NAM where a macrophage-mediated muscle fiber necrosis causes devastating muscle destruction, not muscle fiber atrophy. Although not pathogenic, anti-SRP and anti-HMGCR antibodies remain important disease markers of diagnostic value because they are detected in up to 65% of NAM patients [1].

Polymyositis and Inclusion-Body Myositis

In PM and IBM, $CD8^+$cytotoxic T cells surround and invade healthy, non-necrotic muscle fibers that aberrantly express MHC-I [1-3,50-53]. MHC-I expression, absent from the sarcolemma of normal muscle fibers, is probably induced by cytokines secreted by activated T cells. The CD8/MHC-I complex is characteristic of polymyositis and inclusion-body myositis and its detection aids in confirming the histologic diagnosis [2-5,50-53]. The $CD8^+$ T cells contain perforin granules directed towards the surface of the muscle fibers, resulting in myonecrosis upon release [54,55]. Analysis of T-cell receptor molecules expressed by the infiltrating $CD8^+$ T cells reveals clonal expansion of T-cell receptor chains and conserved sequences in the antigen-binding region, suggesting an antigen-driven T-cell response [56-58]. This is further supported by the expression of co-stimulatory molecules and upregulation of adhesion molecules, chemokines, and cytokines [59-61]. Chemokines and cytokines, including interleukin-6, 8,10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1a (MIP-1a), or IP-10 and its receptors, are expressed in the endomysial inflammatory cells and the neighboring extracellular matrix and may enhance leukocyte recruitment, trafficking and activation [62]. Adhesion of lymphocytes to muscle may be facilitated by metalloproteinases, which are expressed on the autoinvasive CD8+ T cells and make cell-to-cell contact with muscle fibers [1,17,63,64]. There is also B-cell activation, most prominent in IBM [65] as supported by the presence of *anti-cytoplasmic 5'-nucleotidase 1A (cN1A; NT5C1A)* autoantibodies directed against the cN1A nuclear protein involved in RNA processing [31]. These antibodies are not however pathogenic or IBM-specific but simply denote the autoimmune dysregulation in IBM muscles. Plasma cells and myeloid dendritic cells, potent antigen-presenting cells, are also seen among the endomysial infiltrates of patients with PM, DM, and IBM [66] but their significance is still unknown.

Non-immune factors in Inclusion Body Myositis and cross-talk between inflammation degeneration and muscle autophagy

Inclusion-body myositis is a complex disorder because, in addition to the afore-mentioned autoimmunity, there co-exists an important degenerative component, highlighted by the presence of congophilic amyloid deposits within some fibers [18,20,66,67]. Similar to Alzheimer's disease, these deposits immunoreact against amyloid precursor protein (APP), β-amyloid, apolipoprotein-E, α-synuclein, presenilin, ubiquitin, and phosphorylated-tau attesting to protein aggregation [18,20,66]. Immunostaining for the ubiquitin or tau components, TDP43 and p62, has been even advocated as

Table I. A step-by step approach in the treatment of inflammatory myopathies: 2020 and beyond.

Dermatomyosits (DM) [1-3,72-83]
1. High-dose prednisone (oral or intermittent intravenous in acute cases) 2. In steroid-responsive patients add an immunosuppressant [mycophenolate, (most preferable) azathioprine, or methotrexate] 3. High-dose intravenous immunoglobulin (IVIg) if steps 1-2 fail 4. Rituximab, if IVIg is not sufficiently effective 5. Consider new biologics including eculizumab, other anti-B cell agents or JAK inhibitors 6. Most promising future: anti-complement agents such as eculizumab, ravulizumab (ultomiris), zilucoplan
Polymyositis (PM) [1-3,72-83]
1. High-dose prednisone (oral or intermittent intravenous in acute cases) 2. In steroid-responsive patients add an immunosuppressant [mycophenolate, (most preferable) azathioprine, or methotrexate] 3. High-dose intravenous immunoglobulin (IVIg), if steps 1-2 fail 4. Rituximab, if IVIg is not sufficiently effective 5. If above unsatisfactory, reconsider the diagnosis and explore it with a new muscle biopsy
Necrotizing Autoimmune Myositis (NAM) [1-3,72-83]
1. High-dose prednisone (intravenously 1g/daily for 5 days may be needed in acute cases) 2. High-dose intravenous immunoglobulin (IVIg) 3. Rituximab, if IVIg not sufficiently effective 4. Consider new biologics, including eculizumab, other anti-B cell agents or JAK inhibitors 5. Most promising future: anti-complement agents, such as eculizumab, ravulizumab (ultomiris), zilucoplan
Anti-synthetase syndrome-Overlap Myositis (Anti-SS-OM) [1-3,72-83]
1. High-dose prednisone (oral or intermittent intravenous in acute cases) 2. In steroid-responsive patients add an immunosuppressant [mycophenolate, (most preferable) azathioprine, or methotrexate] 3. High-dose intravenous immunoglobulin (IVIg) if steps 1-2 fail 4. Rituximab, if IVIg is not sufficiently effective 5. If interstitial lung disease, may also consider cyclophosphamide
Inclusion Body Myositis [1-3,84-92]
1. Physical therapy; CoQ10; encourage participation in a controlled study 2. If dysphagia is prominent, IVIg 3. All trials with immunosuppressants, immunomodulating agents, muscle growth factors TGF-β inhibitors have failed. Among them, most promising was alemtuzumab in an uncontrolled study

diagnostic markers [1,18,67]. It remains however unclear, how these proteinacious aggregates, which are also seen in other vacuolar myopathies, induce an inflammatory myopathy and what triggers disease, inflammation or protein aggregation [1,20]. Laser microdissection of T-cell-invaded fibers, compared to non-invaded or vacuolated ones, has revealed differential upregulation of inflammatory signaling such as interferon-γ-receptor [68]. Compelling evidence suggests that aging, abnormal proteostasis (the network controlling proteins) [1,28,20], cell stress induced by MHC-1 or nitric oxide, long-standing inflammation and proinflammatory cytokines like interferon-γ and IL1-β [69-70], may cumulatively trigger or enhance degeneration leading to further accumulation of stressor molecules and misfolded proteins [1,69-71].

Treatment of DM, PM and NAM (Tab. I)

Oral prednisone 1 mg/kg, or up to 100 mg per day, as a single daily dose is the first-line drug based on experience, but not controlled trials [1-6,17,72,73]. Some clinicians prefer adding an immunosuppressant from the outset. In patients with severe or rapidly worsening disease, intravenous methylprednisolone 1 gm/kg for 3-5 days is preferable before starting oral glucocorticoids. After 3-4 weeks, prednisone is tapered as dictated by the patient's response, preferably by switching the daily dose to alternate-days [1-3]. If by then objective signs of increased strength and activities in daily living are absent, tapering is accelerated to start the next in-line agent. A tactical error is the practice of "chasing" the CK level as a sign of response, especially in patients reporting a sense of "feeling better" but not necessarily stronger. When the strength improves, the serum CK drops, but fall in CK alone is not a sign of improvement [1-3].

In glucocorticoid-responsive patients, *azathioprine*, *mycophenolate mofetil, methotrexate* or *cyclosporine* are empirically used for "steroid-sparing" [1-3, 17,72,73]. When

interstitial lung disease co-exists, *cyclophosphamide* or *tacrolimus* may be helpful [74]. When glucocorticoids fail to induce remission or in rapidly progressive cases, *intravenous immunoglobulin* (IVIg) 2 gm/kg is appropriate [1-3;69,70,73]. In a double-blind study, IVIg was effective in refractory dermatomyositis [75]; monthly infusions may be required to maintain remission. In open-label trials, IVIg also seems effective in polymyositis and necrotizing autoimmune myositis[1-3,17,75]. Subcutaneous Ig appears to sustain remission (Tab. I) [76].

If glucocorticoids and IVIg have not helped, the diagnosis should be revisited, and a repeat muscle biopsy might be considered. If the diagnosis is re-confirmed, biologics approved for other immune diseases are further options [1-3,70,73]. Among those, the first is *rituximab* (anti-CD20 antibody), which at 2 gm (divided in two bi-weekly infusions) seems effective in several dermatomyositis, polymyositis, and necrotizing autoimmune myositis patients. A placebo-controlled study in 200 patients however, did not meet the primary end-point largely because of study design; although at week 8 there was no difference between placebo and rituximab, at week 44 when all patients had received rituximab, 83% met the definition of improvement [77,78]. Patients with anti-Jo-1, Mi-2, or anti-SRP antibodies are also likely to respond [78,79,80]. *TNF inhibitors* (infliximab, adalimumab, etanercept) are ineffective and may worsen or trigger disease [1,17]. Tocilizumab and IL-1b inhibitors may be of help in small case series [81,82]. Among the new biologics, *anti-complement C5 (eculizumab),* should be very promising especially in dermatomyositis where complement plays a major role in microangiopathy and muscle fiber necrosis. Eculizumab may be also effective in NAM but controlled studies have not been done. Overall, the long-term outcome of treatment for inflammatory myopathies has substantially improved, with a 10-year survival at > 90% [83]. A step-by-step therapeutic approach in all IM subsets is provided in Table I.

Immunotherapies for IM during COVID-19

Patients with IM have been justifiably concerned as to whether their disease status adds an additional risk placing them into an "immunosuppressed or immunocompromised" category. As discussed previously [36], there is no evidence that the inflammatory myopathy itself makes them more susceptible to COVID-19 or the immunosuppressive therapies they are receiving have such a potential. If clinically stable and not lymphopenic, there is no data-driven reasons to change anything and disturb clinical stability. For patients on monthly IVIg, there may be even a theoretical advantage that IVIg offers additional protection due to natural autoantibodies [36]; if IVIg is not infused as home-infusion, switching to self-administered subcutaneous IgG might be an option to diminish exposure. For patients on rituximab, the infusion intervals can be prolonged to more than 6 months, because both, B-cell reduction and clinical benefit, can persist longer [36].

Treatment of Inclusion-Body Myositis

Because of T-cell-mediated cytotoxicity and the enhancement of amyloid aggregates by pro-inflammatory cytokines as outlined earlier, immunosuppressive agents have been tried in IBM but all failed probably because the disease starts long before patients seek medical advice, when the degenerative cascade is already advanced and inflammatory mediators have enhanced degeneration and autophagy [1-3,17,84-86]. Glucocorticoids, methotrexate, cyclosporine, azathioprine or mycophenolate are ineffective and, although some patients initially experience mild improvements, there is no long-term benefit [1,17,84]. IVIg is ineffective in controlled trials but may transiently help some patients, especially those with life-threatening dysphagia where is the treatment of choice based on statistically significant changes in the controlled trial [87,88]. Alemtuzumab may provide short-term stabilization [89] but a controlled study is needed. A*nti- IL1-receptor (Anakinra)* [90] and IL1 receptor antagonist (Ilaris) also failed [91]. Trials targeting muscle-inhibiting TGF-β molecules or muscle growth factors are also disappointing and doubleblind studies have been clearly negative[92]. Although life expectancy seems normal, most patients with end-stage disease require assistive devices such as cane, walker, or wheelchair [22]. Dysphagia can be life threatening if IVIg has not helped.

Evolution of the IM field in the context of the Mediterranean Society of Myology (MSM) with a personal tribute to G. Nigro

Inflammatory myopathies have been discovered and subsequently studied by Neurology scholars with expertise in neuromuscular pathology fostering progress in muscle immunopathology, disease recognition, subset subtyping and pathogenesis. Over the last 30 years the very best minds and Neurology scholars in this field with leaders like W King Engel, Valerie Askanas, Andrew Engel, George Karpati, Victor Dubovitz and many others from USA, Italy, France, Australia, Israel etc. have participated on a regular basis in the MSM meetings. I have had the chance to be there every year almost since the creation of the MSM and have hosted two such events in Greece, one in Corfu and another one in Athens. Writing

this piece in the memory of Giovani Nigro brings back a blend of unique pleasantries of good science and humour in a relaxing and friendly atmosphere of picturesque environments and scholarly, formal, and informal, discussions about inflammatory myopathies. Being honoured by Giovanni in his unique style at the gala dinner among the best of friends and neuromuscular colleagues was the epitomy of the MSM that I will never forget.

This opportunity in honouring the memory of Giovanni Nigro and the unique meetings he has organized and overseen, is also an introspective on the future of the IM field as it is now moving from the neuromuscular clinicians/scientists that splendidly served it for years and advanced the field, to other subspecialties with different training backgrounds. We have all witnessed the last few years that neurologists with muscle pathology and immunopathology training are becoming increasingly scarce as very few of us continue to keep an active muscle pathology laboratory. Muscle biopsies are mostly performed now by surgeons, read by general pathologists either on paraffin sections with just the very basic – if any – immunopathology or enzyme histochemistry stains on fresh-frozen sections, and without knowledge of the clinical neuromuscular evaluation. The lack of clinicopathologic correlation, a fundamental principle of a neuromuscular neurologist for the diagnosis of myopathies, as pioneered by WK Engel and taught all of us, may be impacting on the identification of the correct inflammatory myopathy subtype and the distinction from dystrophies. We had been proud of our unique expertise to precisely assess and quantify the patient's muscle strength, being aware on how best to distinguish the contribution of functional weakness or pains from true muscle weakness, and bring this to diagnostic fruition by personally performing muscle biopsy, selecting the muscle to biopsy, looking at the slides and, after combining clinical with histology, initiate proper therapy. Concurrently, research on expanding the diagnostic muscle histopathology, immunopathology or molecular muscle pathology had flourished. Today, most clinicians involved in the diagnosis and care of patients with IM are of different subspecialties with different training backgrounds, such as rheumatologists, rheumatoneurologists or neurologists/elctromyographers. The prior focus on myopathology and molecular muscle immunopathology is slowly being shifted to serology, circulating humoral factors and antibodies, and muscle imaging. Whether will prove more fruitful remains to be seen.

Serving for more than 40 years as head of Neuromuscular service with still a fully functioning laboratory and having trained more than a hundred neuromuscular fellows around the world, I am also witnessing the directional shift of our neuromuscular trainees who are mostly centered around electromyography. We are not however to blame; it is economics that has prevented the maintenance of active neuromuscular pathology laboratories in many Universities. As a result, previously flourishing regional myology meetings, such as the MSM under Dr Giovanni Nigro's leadership, have vanished as if there is not need to have them; electromyographers go to electrophysiology meetings, rheumatologists to rheumatology meetings and general neurologists to neurology meetings.

Writing this in honouring of Giovanni Nigro' memory, I remain with the pleasant memories of blending the many years of myology progress with innovative discussions about culture and civilization with stimulating leaders in the clinical and basic science of muscle diseases. These unforgettable memories in the middle of the COVID-19 pandemic bring me back to the sad reality that the wonderful Giovanni Nigro's era of the MSM may never return; yet at the same time, as the sun comes after a storm, these memories also bring shining hopes on how Giovanni's legacy will build a bright future for our field. After the COVID-19 pandemic ends, we should be all armed with enthusiasm, determination and organizational to re-build the society from where it started, teach the new generation of neuromuscular experts what we have all learnt, and provide them with the stimulus on how best to combine the excellence in the clinic with histopathology, immunology, immungenetics and molecular biology to advance the filed towards effective target-specific therapies. Afterall, the advances in molecular science and means of communication are on our side. This will be Giovani's best legacy.

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