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ScienceDirect

Neuromuscular Disorders 30 (2020) 70–92

www.elsevier.com/locate/nmd

Workshop report

239th ENMC International Workshop: Classification of dermatomyositis, Amsterdam, the Netherlands, 14–16 December 2018

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Received 9 September 2019

1. Introduction

Organizers of this 239th ENMC workshop welcomed 22 participants from 12 countries worldwide (Belgium, Canada, China, the Czech Republic, France, Germany, Japan, The Netherlands, Spain, Sweden, the United Kingdom, and the United States of America) to Amsterdam on 14–16 December 2018 for this workshop on the clinicopathological classification of dermatomyositis (DM).

Idiopathic inflammatory myopathies (IIM) are a heterogenous family of diseases that can affect the muscles, skin, lungs, and joints. There have been prior attempts to classify IIMs, including the highly influential classification criteria for DM, polymyositis (PM), and immune-mediated necrotizing myopathy (IMNM) resulting from the 119th ENMC workshop in 2003 [1]. However, over the last 15 years, considerable progress has been made in our understanding of the IIMs that requires re-evaluation and re-formulation of the earlier ENMC criteria. In particular, myositis-specific autoantibodies are now recognized to define unique subgroups of IIM. Although a data-driven classification system for IIM was recently endorsed by the American College of Rheumatology and the European League Against Rheumatism [2,3], that system does not include autoantibody-defined subgroups. We recently proposed a classification system for IMNM that includes autoantibody-defined subgroups at the 224th ENMC workshop [4]. Here we propose to extend these efforts by arriving at modernized classification criteria for DM and its subsets based on international consensus. To this end, a team of 22 experts assembled to address the following goals:

- Consensus regarding a valid definition of DM
- Consensus regarding a definition of DM diagnostic criteria (clinical and pathological)
- Presentation and discussion about animal-models suitable for future research on DM
- Consensus on the role of serology in DM
- Proposition and discussion of treatment schemes for DM (given the absence of clinical trials).

2. DM subtypes

Over the last few decades, several DM-specific autoantibodies have been discovered and each of these has been associated with a unique clinical phenotype. Dr. Andrew Mammen opened the workshop with a session describing the clinical features of patients with autoantibodies recognizing nuclear matrix protein (NXP) 2. Initially named "anti-MJ", these autoantibodies were first recognized to exist in ~18% of juvenile DM patients [5]. After the protein target was identified as NXP2 [6], it was shown that these autoantibodies are associated with calcinosis in children with DM [7]. Approximately 17% of adult DM patients have anti-NXP2 autoantibodies and initial reports suggested a possible association with cancer [8]. The association between cancer and anti-NXP2 autoantibodies was confirmed in subsequent studies that also demonstrated an increased

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https://doi.org/10.1016/j.nmd.2019.10.005
0960-8966

prevalence of subcutaneous edema, calcinosis, distal weakness, dysphagia, and myalgia compared to adult DM patients without these autoantibodies [9,10]. Another study showed that anti-NXP2-positive juvenile DM patients are weaker and less likely to enter remission than other children with DM [11].

An analysis of muscle biopsies from patients with different DM-specific autoantibodies revealed that lymphocytes surround and invade myofibers in 28% of muscle biopsies from DM patients with other autoantibodies [12]. However, this pathologic finding was never observed in DM patients with anti-NXP2 autoantibodies. Despite these histological differences in muscle biopsy features, Dr. Mammen presented preliminary data from gene expression profiling studies demonstrating that anti-NXP2 muscle tissue has a prominent type I interferon signature that is indistinguishable from patients with other DM-specific autoantibodies [13].

Next, Dr. Guochun Wang described the clinical features of DM patients with autoantibodies recognizing transcription intermediary factor (TIF)1-γ. Also called TRIM33, TIF1-γ is a multifunctional protein with complex effects on several cellular pathways, including immunoregulation and carcinogenesis [14]. In his Chinese cohort of DM patients, the prevalence of anti-TIF1-γ autoantibodies was 19.2%; no anti-TIF1-γ autoantibodies were found in other types of IIM. Two types of skin rash were observed in patients with anti-TIF1-γ: one is a facial dermatosis which usually comes with long-time disease course; the second type is characterized by a skin rash around the hairline.

Muscle weakness is common in anti-TIF1-γ positive DM. Dr. Wang presented data showing that 77.8% of Chinese patients with anti-TIF1-γ had muscle involvement. Muscle biopsy showed that approximately half of these presented with typical perifascicular atrophy and other DM-associated pathological features, 31% had nonspecific changes, and a small portion (~12%) had normal muscle pathology. Patients with anti-TIF1-γ autoantibodies less infrequently developed interstitial lung disease (ILD) compared with anti-TIF1-γ negative DM patients; of note, the latter group included antisynthetase patients with DM-like rashes. He also noted that ILD in anti-TIF1-γ positive DM was usually relatively mild and that rapidly progressive (RP)-ILD was rare. Dysphagia occurred in 43% of Chinese patients with anti-TIF1-γ autoantibodies.

A striking clinical feature of patients with anti-TIF1-γ is an association with cancer. In the Chinese cohort studied by Dr. Wang, 55% had malignancy. Moreover, among those with cancer-associated-myositis, 64% were positive for anti-TIF1-γ autoantibodies. Compared with the age- and sex-matched Chinese population, the incidence of cancer in anti-TIF1-γ positive patients was markedly increased (SIR value= 17.82) [15]. These results are consistent with a meta-analysis conducted by Prof. Albert Selva-O'Callaghan from Spain, which showed that sensitivity and specificity of anti-TIF1-γ autoantibodies for diagnosing cancer in myositis was 78% and 89%, respectively [16].

In a further comparison of the clinical features between anti-TIF1-γ positive patients with and without cancer, the age of the disease onset in the group with cancer was significantly older than that of patients without cancer. Although there was a trend for increased prevalence of dysphagia in patients with cancer, this was not statistically significant. Moreover, other symptoms, including muscle weakness, arthritis, and ILD, were not significantly different between these two groups. Of importance, the survival rate was much lower in patients with cancer than in patients without cancer. Dr. Wang presented unpublished data showing that the 5 years and 10 years survival rates in the Chinese anti-TIF1-γ DM patients with cancer were only around 60% and 40%, respectively. In contrast, the 5 years and 10 years survival rates were higher in the patients without cancer (both>90%).

Dr. Océane Landon-Cardinal presented next, explaining that autoantibodies recognizing Mi2 were the first DM-specific serologic marker [17,18]. The prevalence of anti-Mi2 autoantibodies ranges from 2 to 45% in adult DM patients and from 4 to 10% in juvenile DM patients [19]. These autoantibodies have been associated with the "classic" form of DM, with hallmark cutaneous lesions as well as cuticular overgrowth and periungueal hemorrhage [20], mild muscle disease, a low risk of ILD, and a good prognosis with a low risk of cancer [21].

Dr. Landon-Cardinal shared unpublished data from a French cohort of 64 anti-Mi2-positive DM patients that was compared to 55 anti-Mi2-negative DM controls. The presence of anti-Mi2 autoantibodies was associated with an increased prevalence of classic Gottron papules and/or sign and periungueal erythema as well as a lower risk of cutaneous ulcerations ($p \leq 0.05$). These antibodies had been associated with prominent muscle weakness and higher creatine kinase (CK) levels [22]. Consistent with this, more than half of the anti-Mi2-positive patients from the French cohort initially presented with severe muscle weakness (MRC-5 scale $\leq$3). Previous case series have reported a low prevalence of extramuscular features, including Raynaud phenomenon, ILD, and arthritis [22,23]. In the French cohort, however, a third of patients presented with ILD, albeit mostly mild. Arthritis and Raynaud phenomenon were observed in only 10% of anti-Mi2-positive DM patients. Pathological descriptions of anti-Mi2-positive DM have reported an increased prevalence of primary inflammation (i.e., focal lymphocytic invasion of myofibers) [12] and, in children, relatively severe pathological findings based on a validated juvenile DM biopsy scoring system [24–26]. A systematic review of muscle biopsies from the French patients revealed that anti-Mi2-positive DM patients ($n=14$) had increased numbers of diffuse CD68+ dominant inflammatory infiltrates, more necrotic and regenerative fibers, and increased sarcolemmal C5b-9 deposition on non-necrotic fibers compared to anti-Mi2-negative DM controls ($n=32$). Traditionally, anti-Mi2 antibodies have been associated with a good prognosis and low risk of malignancy. Indeed, the presence of these autoantibodies was even suggested to be an exclusion criteria for paraneoplastic myositis [27]. However, in the French

cohort, cancer was found in 22% of anti-Mi2 DM patients within 3 years of diagnosis, with a standardized incidence ratio (SIR) of 5.1 [3.0–8.6] ($p<0.001$). A better prognosis and survival rate has been reported in association with this antibody [22,24]. Nonetheless, a relapsing disease was observed at follow-up in 50% of patients in the French cohort.

Professor Olivier Benveniste presented on the clinical phenotype of DM patients with autoantibodies recognizing small ubiquitin-like modifier activating enzyme (SAE). These autoantibodies are relatively rare, representing only 1–8% of all DM patients. Indeed, only seven case series of anti-SAE-positive DM patients have been published with a total of just 66 patients [28–35]. Adding to these, professor Benveniste presented data on a series of 41 anti-SAE-positive DM patients collected from among several different French Internal Medicine or Dermatology departments. All these patients tested positive for anti-SAE autoantibodies using the Euroimmun line blot which, compared to immunoprecipitation, has been shown to have 100% sensitivity and 99.6% specificity for these autoantibodies [34].

No marked differences were observed between the already reported patients and the new French series. These patients typically present with a classic DM skin rash (i.e., heliotrope rash and Gottron's papules) which is refractory to treatment in more than 50% of the cases. These patients can be amyopathic (20%) and when muscle weakness is present, it is generally mild (proximal muscle strength in the 4–5 range) with an average CK level of 216 IU/L. Nevertheless, swallowing troubles are frequently encountered (40%). ILD is rare (15% in the French series) and, when present, most often has a pattern consistent with organizing pneumonia (with condensations) rather than non-specific interstitial pneumonia. Finally, concerning associated cancer, the number of patients reported in the literature and in the French series is currently too small to draw any definite conclusions.

Both Drs. Yves Allenbach and Guochun Wang described the clinical features of patients with autoantibodies recognizing melanoma differentiation-associated gene (MDA) 5. Speaking first, Dr. Allenbach pointed out that anti-MDA5 autoantibodies were initially found in Japanese DM patients who were predominantly amyopathic but who frequently had ILD [36]. Since then, it has been shown that the prevalence of anti-MDA5 in myositis patients ranges from 4 to 7% in Europe and North-America and from 15 to 20% in Asia [37–39]. Anti-MDA5-positive DM occurs mainly in women (56–88%) [39,40], in the 43–48 years of age range [39,41], and has been associated with defined HLA haplotypes in Asian regions [38,42]. Anti-MDA5 autoantibodies delineate a relatively homogeneous phenotype of DM with predominant extra-muscular manifestations including a high risk of life-threatening lung complications in which the signs of myositis are mild or absent. The phenotype of children with anti-MDA5-positive DM is similar to that of adult DM, although the frequency and the severity of the ILD seem to be lower in children [43].

DM associated with anti-MDA5 autoantibodies is a systemic disease with skin (95–100%), lung (75%), joint (40%), and muscle involvement (40%) associated with constitutional signs (fever 50%). In addition to the classical DM skin rash, patients present frequently with other characteristic skin features including ulcers, palmar papules or mechanic's hands [44]. Another characteristic of the disease is the very high frequency of ILD (50–100%) [39,45] compared to other DM patients. ILD is frequently rapidly progressive [46] explaining the poor survival rate of the disease (59–75%) [40,41]. Moreover, up to two thirds of the patients have polyarthritis [47]. Of note, even though anti-MDA5-positive DM is not associated with an increased risk of malignancy, the disease remains the most severe, in term of mortality, compared to all other forms of myositis.

Among anti-MDA5 positive DM patients, relatively few have muscle weakness (0–55%) [40,46] and the CK levels are relatively low (173–912 IU/L) [40,41]. Consistent with this, myopathological features are mild, and only a minority of the patients have classical DM perifascicular pathology [12,48]. Lymphocytic infiltrates are mild and although these are frequently clustered around vessels, a vasculopathy is not morphologically obvious [48]. Interestingly, anti-MDA5-positive DM shares the same muscle tissue IFN-signature with anti-MDA-negative DM, albeit at lower level [48]. Along with the high IFN-I level in the blood of MDA5-positive patients [49], this suggests a common pathomechanism in anti-MDA5-positive DM as well as in other forms of DM.

Speaking next, Dr. Guochun Wang reminded the audience that MDA5 is one of the retinoic acid-inducible gene (RIG)-like receptors (RLRs) and that many viruses can trigger MDA5's activation. Through a complicated procession, MDA5 activation results in the expression of IFN and the induction of antiviral effector genes to limit virus replication and spread. Thus, MDA5 plays an important role in the host's anti-viral response [50]. Based on this biological role of MDA5, it has been proposed that anti-MDA5 autoimmunity is triggered by virus infection and related to IFN expression. To date, there are several studies confirming that DM patients with anti-MDA5 autoantibodies and other subtypes of DM are strongly associated with increased IFN expression [48,51,52].

In the Chinese cohort described by Dr. Wang, the prevalence of anti-MDA5 autoantibodies was 12.9%. Interestingly, these patients seem to have two clinically distinct mucocutaneous phenotypes. The first is cutaneous ulceration, occurring in as many as 80%. These ulcers have a predilection for certain sites – overlying Gottron papules or Gottron sign on the hand, elbows and/or shoulders. Less commonly, these ulcers may occur on sun-exposed sites such as arms, chest and back. The second mucocutaneous feature associated with anti-MDA5 autoantibodies is alopecia. Fortunately, once disease activity has been controlled, this complication typically improves relatively quickly.

Dr. Wang noted that the prevalence and severity of muscle involvement in MDA5-positive DM varies in different reports [36,44,53,54]. As these reports are derived from DM cohorts on different continents, it is unclear if there is a relation between ethnicity and muscle involvement. However, reports from the Japanese and Chinese groups both show that

there was a lower rate of clinically apparent myositis in anti-MDA5-positive DM compared to American and European cohorts.

The most significant and potentially life-threatening feature associated with anti-MDA5-positive patients is RP-ILD. In the Chinese cohort, 78.9% of the patients had RP-ILD during the disease course [55]. Moreover, a meta-analysis conducted by Dr. Chen et al. showed that the odds ratio for developing RP-ILD was 20-fold higher in anti-MDA5 positive DM patients than in DM patients without these autoantibodies [46]. The radiological features of this type of RP-ILD usually showed perilobular opacities that progressed rapidly to wide consolidation during the course of the disease. Of note, the pathological features of the RP-ILD in anti-MDA5 patients have not been deeply explored. In the few cases reported, most had a diffuse alveolar damage (DAD) pattern at autopsy [56]. Pneumomediastinum and/or subcutaneous emphysema is another severe complication that has been seen in anti-MDA5 patients and these features are associated with poor survival [57].

Importantly, anti-MDA5-positive patients seem to be more susceptible to infection, including severe or fatal pneumocystis jirovecci pneumonia (PJP). In the Chinese IIM cohort, the occurrence of PJP was 3.4%, and 40% of these were from the anti-MDA5-positive group. Both lymphopenia and hyperferritinemia are common laboratory features of anti-MDA5 patients. Regarding the outcome of Chinese patients with anti-MDA5-positive DM, most had poor response to glucocorticoid therapy and needed more aggressive treatment. The 5 year survival rate of the anti-MDA5 patients was only 50.2% in this cohort [58].

In summary, Dr. Wang concluded that although the cutaneous and pulmonary features are different and more severe than seen in other types of DM, anti-MDA5-positive DM should be considered a subtype of DM rather than as a separate disease.

3. Pathological criteria for DM

Professor Jan De Bleecker began by presenting unpublished data from a study evaluating inter-rater variability in muscle biopsy reading in IIM. Despite the fact that most experts in the field acknowledge that muscle biopsy is an important tool in diagnosis and sub-differentiation of the forms of myositis as well as for differentiating autoimmune myositis from muscular dystrophies, other degenerative hereditary myopathies and toxic myopathies, little data is available on standardization and validation of adult patient biopsy findings. Two focused European Neuromuscular Centre (ENMC) workshops led to a consensus on a recommended set of minimal stains for IM biopsy evaluation and a score sheet assessing individual pathological features of muscle biopsies [59,60]. An international group ($n=12$) of experts in IM muscle biopsy reading scored 26 muscle biopsies using a scoring tool that surveyed findings in 4 domains: muscle fiber, inflammatory, vascular and connective tissue [25]. Overall severity of the pathological abnormalities were scored on a visual analogue scale (VAS), and a final diagnosis had to be made from 7 possibilities: DM; PM; inclusion body myositis (IBM); antisynthetase syndrome myositis; IMNM; nonspecific myositis; other. Fleiss' kappa for categorical outcomes was calculated and interpreted as: poor (Ƙ < 0.01); slight (Ƙ 0.01–0.20); fair (Ƙ 0.21–0.40); moderate (Ƙ 0.41–0.60); substantial (Ƙ 0.61–0.80) or near perfect (Ƙ 0.81–1.00).

Inter-rater agreements were often surprisingly low for individual pathological features, even for well-known abnormalities (e.g., slight for fiber necrosis and regeneration, reduced capillary density or membrane attack complex (MAC) staining on capillaries). Agreement was fair for presence of inflammatory cells invading non-necrotic muscle fibers, the presence of perivascular inflammatory cells, and the presence of perimysial inflammatory cells. Moderate agreement was obtained for perifascicular muscle fiber atrophy, perifascicular muscle fiber necrosis, or the presence of fibers with rimmed vacuoles. Almost perfect agreement was reached for the presence of perimysial alkaline phosphatase positivity in connective tissue. The agreement on the general severity score was fair. Moderate agreement was also reached for the final diagnosis (Ƙ = 0.443), a decent inter-rater agreement given that 7 categories were offered. Possible reasons for the poor inter-rater agreements on even routinely assessed biopsy features were discussed along with future plans to improve the scoring sheet [61].

Next, Dr. Ichizo Nishino discussed the pathological features of DM muscle biopsies in a Japanese cohort. He noted that the type I interferon (IFN) signature in DM muscle was first demonstrated by microarray analysis [62] and that this has been subsequently confirmed in several reports. Consistent with this, the upregulation of type I IFN pathway genes was observed on RNAseq analysis on muscle tissue from Japanese DM patients. Among all the proteins encoded by genes constituting type I IFN signature, myxovirus resistance protein 1 (MxA) seems to be the most reliable diagnostic marker for DM [63]. Indeed, its diagnostic potential was recently tested by an international group and showed that MxA was expressed in DM muscles but not in any of 30 antisynthetase syndrome (AS) cases. Dr. Nishino has now tested a much larger number of antisynthetase cases [64]. This revealed that only 3 of 194 AS cases expressed MxA in the muscle. This confirms that muscle MxA expression is highly specific to DM and also suggests that the pathomechanisms underlying DM are distinct from those underlying AS even though the latter entity is often diagnosed as DM [65]. Dr. Nishino suggested that DM should be redefined as a type I interferonopathy and that AS is a separate disease.

Dr. Nishino also described a study in which his group characterized the myositis-specific autoantibodies present in the serum of 98 consecutive DM cases analysed between June 2015 and December 2018 and who had MxA-positive muscle pathology. Interestingly, DM-specific autoantibodies recognizing TIF1-γ, MDA5, Mi2, NXP2 and SAE were present in all but 3 of these cases, indicating

a tight association between DM-specific autoantibodies and myofiber MxA expression. Dr. Nishino proposed that these autoantibodies are a biomarker of muscle type I interferonopathy.

Of note the prevalence of perifascicular atrophy varied according to DM-specific autoantibody status in the Japanese population. This histological feature was present in 91% of those with anti-Mi2, 45% of those with anti-TIF1-γ or anti-NXP2, and only 11% of those with anti-MDA5 autoantibodies.

It has been reported that myofiber MHC-II expression is more frequent in AS (81.8%) than in DM (23.5%) and that its perifascicular expression pattern was specifically seen only in AS but not in DM [66]. Among 194 AS and 95 DM cases in the Japanese cohort, MHC-II was expressed in 53% and 29% of cases, respectively. Interestingly, however, perifascicular MHC-II expression was seen not only in AS cases (36% in all AS, most common in anti-Jo1 [61%]) but also in DM cases (14%). This was the case in anti-NXP2-positive DM (34%) but much less frequent in anti-TIF1-γ (9%), anti-Mi2 (9%) and anti-MDA5 DM (6%).

Sarcolemmal MAC deposition is considered a pathological marker indicative of immune-mediated muscle fiber necrosis. It was seen in 73% of anti-Mi2 DM cases but much less frequently in other subtypes such as anti-TIF1-γ [24%], anti-NXP2 [9%] and anti-MDA5 [6%]. This is consistent with the observation that the percentage of necrotic fibers and CK levels are highest in anti-Mi2 DM cases and lowest in anti-MDA5 DM.

Perimysial connective tissue fragmentation and alkaline phosphatase expression are reported to be characteristic pathological features of anti-Jo-1 myopathy [67]. In a Japanese cohort, perimysial connective tissue fragmentation was seen in 63% of AS patients but also in 59% of DM cases – most frequently in anti-Mi2-positive DM (91%). Likewise, perimysial alkaline phosphatase activity was seen in 42% of AS and 32% of DM cases, respectively, with the highest frequency in anti-Mi2-positive DM (91%) among all DM subtypes.

Microinfarction was seen in 2.8% of adult and 28.6% of juvenile DM (JDM) cases, indicating that JDM cases are at a 10 times higher risk for microinfarction. Interestingly, none of the microinfarction cases was positive for anti-Mi2 antibodies (although the number of cases was too small to draw definite conclusions).

Dr. Nishino concluded by noting that type I IFN signaling in muscle is tightly associated with the DM-specific autoantibodies (i.e., those recognizing TIF1-γ, MDA5, Mi2, NXP2 and SAE) but not with antisynthetase autoantibodies (e.g., those recognizing Jo1). Therefore, DM should be considered as a separate disease than AS with the former redefined as a type I interferonopathy. Furthermore, the pathological features of each subtype of DM seem to be different. Most strikingly, anti-Mi2 DM is characterized by perimysial pathology, perifascicular atrophy, sarcolemmal MAC deposition, and is the least associated with microinfarction.

Next, Professor Werner Stenzel discussed pathology parameters that can be useful to differentiate DM from other forms of myopathy. He noted that from a purely morphological point of view, DM is heterogeneous and that this fact has long been recognized, discussed, and tried to be understood in terms of implementing characteristic diagnostic biopsy-criteria. He suggested that understanding the pathophysiology of DM could be based on parameters visible under the microscope or more recently by modern analytical methods using muscle biopsy samples such as tissue-based transcriptomics, proteomics, RNA-sequencing, genomics and combinations of these techniques in the future.

In the following session, Dr. Stenzel discussed the experience in Berlin with regard to the association of certain muscle biopsy features with different DM-specific autoantibodies. As muscle involvement is frequently patchy in anti-MDA5 DM, pre-biopsy localization of most affected muscle tissue may be especially warranted in these cases. Similarly, within a biopsy sample, pathological changes may be confined to a certain area, while the rest of the biopsy may look rather minimally affected on H&E stains. However, staining for MHC class I, CD56, or neonatal myosin can highlight focal areas next to affected areas with sparse perimysial and perivascular cell infiltrates. Importantly, in anti-MDA5-positive DM, a putative myoprotective mechanism has been identified by co-expression of iNOS and HSP70 in these areas [48].

The biopsy features of anti-Mi2-positive DM patients include characteristic atrophic fibers mostly confined to perifascicular regions and other areas featuring less structured areas of atrophic fibers admixed with scarce necrotic myofibers; atrophic fibers are never localized exclusively in the perifascicular region. Usually, these biopsies show abundant lymphocytic infiltration, mostly localized to the perimysium and located around vessels; however, there is no leukocytoclastic vasculitis. In addition, numerous B cells, frequently clustered together in perimysial areas often adjacent to larger perimysial vessels, can be identified in these biopsies. Perifascicular pathology can be highlighted by MHC class I staining that shows a characteristic gradient towards the centrofascicular region and also by stains informative about regenerative processes partly featuring the peri-towards centrofascicular gradient but partly showing a more focal and more randomly distributed pattern of positive staining. MAC is predominantly positive on the sarcolemma of myofibers and not on the capillaries.

Anti-TIF1-γ-positive DM cases have distinctive morphologic features including large areas of atrophic fibers at the edge of numerous fascicles, affecting whole fascicles, and extending deeply into the center of the fascicles. Many of these atrophic fibers also have so-called punched-out vacuoles, which, at variance with the rimmed vacuoles in IBM, do not show violaceous lining by Gömöri staining, and often harbor cytoplasmic bodies. These areas also feature ‘ghost fibers’ with ATP-ase 9.4 (faint or even absent staining), and prominent cytochrome oxidase (COX)-paleness (greyish to pale-blueish discoloration) in combined

COX- (succinate dehydrogenase) SDH stains. Most strikingly, these biopsies show predominant MAC deposits on capillaries, which is often pronounced fascicle-wise, and deposits on the sarcolemma may be less prominent. Staining for MHC class I is strongly positive and often shows a peri– towards centrofascicular gradient. Professor Stenzel emphasized that this combination of different patterns along with a positive TIF1-γ autoantibody is highly suggestive of cancer-associated adult DM, which has also been highlighted in a larger Japanese study [68].

Anti-NXP2-positive DM patients also harbor characteristic features in their biopsies, which may be summarized by perifascicular pathology highlighted by MHC-class I staining, atrophic fibers confined to the perifascicular region, and MAC stain on capillaries and also on the sarcolemma. Anti-NXP2 patients can exhibit focal areas of necrotic fibers similar to regional ischemic processes, and this is mostly seen in patients with very high CK levels, acute clinical presentation and predominantly in children.

Anti-SAE-positive biopsies are not yet available in large-enough quantities to draw any conclusions for morphological analysis.

Analyzing different subgroups of DM muscle biopsies, Werner Stenzel emphasized that 7 of the most relevant type I IFN signature genes were similarly elevated in a qPCR study in all subforms of DM and also in DM without any known autoantibody, highlighting that the type I IFN signature is a useful unifying pattern for all DM subgroups and can be used to differentiate DM from other diseases.

Dr. Josefine Radke discussed whether performing a muscle biopsy is necessary to make a diagnosis of DM. She reminded the audience that IIMs are a heterogeneous group of systemic diseases that manifest with muscle inflammation and weakness as well as elevated muscle enzymes. Extramuscular manifestation with involvement of different organs, e.g., the lung, or the skin is common. The most common type is DM. Patients typically present with symptoms including sub-acute to chronic proximal weakness and with a variety of characteristic skin manifestations. Further laboratory investigations, including increased serum creatine kinase (CK) levels and the presence of myositis-specific antibodies (MSA) help to confirm and specify the subtypes.

Despite the above considerations, Dr. Radke concluded that a muscle biopsy followed by histological evaluation remains the gold standard for diagnosing DM, especially since multiple clinical presentations may overlap with possible differential diagnoses with similar clinical presentation which might be missed. These include rare phenotypes such as IgG4-related myositis and brachio-cervical inflammatory myopathy (BCIM). In addition, histological evaluation of a skeletal muscle biopsy may also inform about the different subtypes of DM. Lastly, a correct diagnosis may be suggested by muscle histology in patients with a non-inflammatory myopathy who happen to have false positive myositis autoantibody testing.

On the other hand, a muscle biopsy is an invasive procedure and complications can occur, which may include a hematoma or infection at the biopsy site, or complications due to general anesthesia in children. Therefore, the indication for a muscle biopsy needs to be critically discussed. Following an intensive discussion regarding the pro and cons of the necessity of a muscle biopsy in DM, most participants concluded that in patients with a typical clinical picture and DM-specific autoantibodies, a diagnosis of DM can be made and the muscle biopsy may be omitted. In contrast, if the clinical picture is atypical or DM-specific autoantibodies are absent or not conclusive, a muscle biopsy is still needed to secure the diagnosis of DM.

4. Cancer and DM

Dr. Lisa Christopher-Stine reviewed evidence regarding the association between DM and malignancy. She noted that among the different forms of myositis, DM has the highest risk for an associated cancer, with 10–20% of patients being diagnosed with cancer-associated myositis (CAM) [69], defined as cancer occurring within two years before the onset of myositis or no more than three years afterwards [70].

The increased risk of cancer in DM varies across cohorts, with SIRs in the range of 2.4–6.5 [71]. The salient clinical and laboratory features associated with malignancy are older age at onset, male sex, more severe skin disease, elevated CRP, and/or elevated ESR [71]. A recently reported clinical feature closely associated with malignancy and found exclusively in patients with anti-Tif1-γ autoantibodies is an asymptomatic, well-demarcated, erythematous patch on the posterior hard palate. These “ovoid palatal patches” do not ulcerate and frequently contain white macular markings and a symmetric arcuate configuration across the midline [72]. In contrast to the aforementioned clinical features, DM patients with ILD, arthritis, and Raynaud’s phenomenon have a decreased risk of cancer [71].

To date, DM-specific autoantibodies anti-Tif1-γ and anti-NXP2 have the strongest known link to malignancy. In one study of the Hopkins cohort, patients with either one of these autoantibodies had an increased risk of cancer with an odds ratio of 3.78 (95% confidence interval 1.33–10.8). Stratification by sex revealed that anti-NXP2 was specifically associated with cancer in males with an odds ratio 5.78 (95% confidence interval 1.35–24.7) [8]. A subsequent study of the Hopkins cohort confirmed that anti-NXP2-positive patients have increased cancer risk [9].

In one Japanese cohort, the frequency of cancer in anti-SAE-positive patients was significantly higher than in the anti-SAE-negative patients (4/7 vs. 18/143, $P < 0.0093$) [32]. Although ILD is usually associated with protection from cancer, in one study, 5 of 35 (14%) anti-SAE antibody-positive patients had both ILD and malignancy [73].

Dr. Christopher-Stine next reviewed a conceptual model of the antitumor response as a trigger of DM, analogous to one recently proposed to occur in systemic sclerosis [74]. According to this model, DM autoantigens (especially those associated with cancer) are modified in malignant cells (e.g., overexpression, gene mutation, ectopic expression, and/or posttranslational modification). These modifications lead to

the development of autoantigen-specific T and/or B cell antitumor response. Subsequently, cross-reactivity and/or epitope spreading leads to loss of tolerance against the native protein, promoting an autoimmune response against healthy tissues such as muscle and skin [75].

Dr. Albert Selva-O'Callaghan elaborated further on the mechanisms of cancer risk in patients with DM. Epidemiological evidence has shown that at least one-third of patients diagnosed with DM develop a malignancy within 3 years after the diagnosis [76,77]. Although certain neoplasms may be overrepresented, any type of cancer can be associated with DM [78]. The pathogenesis underlying this association is not well understood, but three mechanisms have been proposed: molecular mimicry, tumor cell DNA mutations, and activity of the checkpoint inhibitor pathway.

Casciola-Rosen et al. found that some antigens were overexpressed in muscle of DM patients and also in some types of cancer, such as breast and lung cancer [79]. This seems to be the case for the Mi2 antigens. T and B cells target these antigens and generate anti-Mi2 antibodies which could cross-react between cancer and muscle. This would lead to the development of inflammatory muscle disease by means of molecular mimicry.

Another proposed mechanism is related to DNA mutations detected in some tumor cells. These mutated genes synthesize slightly different proteins, which act as neoantigens and generate a sustained immune response against the tumor that cross reacts against our own tissues, producing autoimmune diseases such as DM. In an elegant study, Joseph et al. found that mutations in the POL3RA gene, which encodes RNA polymerase III, synthesize a neoantigen that is recognized by the patient's immune system and leads to production of anti-RNA polymerase III, a well-recognized autoantibody found in patients with cancer-associated systemic sclerosis [74]. A cross-reactive immune response between the tumor and normal human tissues was suggested by the authors. This mechanism has also been postulated in patients with cancer-associated DM. A recent study found that patients with anti-TIF1-γ, an autoantibody highly associated with cancer-associated DM, showed a larger number of gene changes (mutations and loss of heterozygosity [LOH] in TIF1 genes) than DM patients testing negative for anti-TIF1-γ autoantibodies [80]. In these cases, the immune response against cancer seems to produce two different scenarios: the strong immune response abates cancer and it disappears, or the malignancy adapts by means of cancer immunoediting and LOH, deleting the mutated gene and selecting more aggressive tumor cells, which leads to the poorest outcome in these patients. In either of these two cases, the immune response shifts from cancer (eliminated or transformed) to tissues expressing high levels of TIF1-γ, mainly muscle and skin. As the damaged muscle expresses additional TIF1-γ [80], a deleterious positive biofeedback effect would propogate the disease.

The final proposed mechanism of the cancer-myositis association involves the checkpoint inhibitor pathway. PD-1/PD-1L is a well-known physiological inhibitory pathway that downregulates the immune system to allow self-tolerance. Blockade of this pathway with the use of monoclonal antibodies such as ipilimumab or pembrolizumab enhances the immune response against the tumor and improves the outcome in diseases such as melanoma and non-small-cell lung cancer. The mutational burden and stroma-tumor infiltrating lymphocyte (str-TIL) density are biomarkers of a good response to checkpoint inhibitors. It has been suggested that soluble-PD-1L, considered a surrogate of checkpoint inhibitor activity, is increased in patients with cancer-associated DM [81]. It remains to be demonstrated that tumors in DM patients show a high mutation burden together with high str-TIL density or PD-1/PD-1L expression. If this is the case, our approach to treatment of the cancer and myositis occurring in patients with cancer-associated DM will change.

Next, professor Olivier Boyer reviewed the association of DM with cancer. He noted that the link between adult DM and cancer had been established by numerous studies [71,78,82,83] and recent meta-analyses [84,85]. In contrast, cancer rarely, if ever, occurs in children with DM. The risk of cancer in adult DM is strongly correlated with the presence of autoantibodies, most notably to anti-TIF1-γ autoantibodies with a rate of associated malignancy of more than 50%. TIF1-γ is the third member of the TIF1 protein family which also includes TIF1-α and TIF1-β [16,86]. Interestingly, TIF1-γ is involved in cellular pathways of tumor promotion [75]. Is the autoimmune status in DM a background for cancer development or, alternatively, may cancer elicit DM?

In support of the second hypothesis, Professor Boyer discussed the model previously reviewed by Dr. Christopher-Stine. Furthermore, along these lines, he presented preliminary results from his group revealing point mutations in the TRIM33 gene by next generation sequencing of tumor DNA from a small series of DM patients.

He next reported on his group's recent investigations aimed at determining whether a distinct type of anti-TIF1-γ autoantibody response, different from that seen in juvenile DM, might be associated with cancer among adult DM patients [87]. For this, his group developed a quantitative anti-TIF1-γ Addressable Laser Bead Immuno-Assay (ALBIA) that allows for the determination of autoantibody levels and isotypes. First, they found that the distribution of autoantibody isotypes was very different between adult and juvenile DM patients with anti-TIF1-γ autoantibodies. Whereas the IgG4 isotype was almost always present in children with DM, this isotype was never found in adult DM patients. The most striking result of this multicenter French study was that one anti-TIF1-γ autoantibody isotype, IgG2, was significantly associated with the occurrence of cancer and increased mortality in adult DM patients. Indeed, high levels of the IgG2 isotype had a 100% positive predictive value of cancer. Multivariate analysis revealed that age greater than 60 years and the presence of anti-TIF1-γ IgG2 were independently associated with mortality. Interestingly, no cancer developed after two years in either anti-TIF1-γ $IgG2^+$ or $IgG2^-$patients, suggesting that intensive screening for neoplasia in adult DM patients with anti-TIF1-γ autoantibodies may not be

required after 2 years of follow-up. The workshop participants concluded that anti-TIF1-γ IgG2 may represent a potential new biomarker of cancer and, as such, agreed on the perspective of conducting a multicenter international study on this subject.

5. Pathophysiology of DM

Dr. Janine Lamb (Manchester, UK) reported on genetic risk factors in DM. The first comprehensive genomewide association study (GWAS) of DM was conducted by the Myositis Genetics Consortium (MYOGEN). This study of 1178 adult- and juvenile-onset individuals of European ancestry identified the human leukocyte antigen (HLA) region as the most significantly associated, but also identified association with genes implicated in other autoimmune disorders [88]. A follow up study carried out using the Illumina Immunochip array identified the most significant association to HLA-B*08:01 ($p = 2.46 \times 10^{-42}$, Odds Ratio (OR) 1.9, 95% Confidence Interval (CI) 1.66–2.17) in 879 adult-onset DM, with independent association to HLA-DQB1*04:02 and a significant amino acid association at HLA-DQB1 amino acid position 57 ($p = 8.95 \times 10^{-14}$) [89]; this amino acid also has been reported as a risk factor for type 1 diabetes. In 471 cases with juvenile-onset DM, the most significant association was to HLA-DRB1*03:01, with independent association to HLA-C*02:02, suggesting that the genetic risk variants underlying juvenile and adult-onset DM may differ [89].

A recent study reported the role of copy number variation of the complement C4 gene and C4A deficiency in JDM [90]. The first GWAS in 576 individuals of Japanese ancestry did not identify genomewide significant association to the HLA region, but did identify association in 33 individuals with clinically amyopathic DM to a splicing variant of the *WDYF4* gene ($p = 1.5 \times 10^{-8}$, OR 3.87, CI 2.23–6.55) that created a truncated *WDYF4* isoform [38]. Functional studies showed that *WDYF4* increases NF-κB activity, interacts with pattern recognition receptors, causes altered MDA-5 signalling and increases MDA5-induced apoptosis [38]. Whilst only nominal association to this gene was identified in 21 clinically amyopathic DM individuals of European ancestry, this could be explained potentially by differences in the relative frequency of MDA5 autoantibodies in these individuals between the Japanese and European populations (72% vs. 0% of those tested, respectively).

Given that myositis autoantibodies define more clinically homogeneous subgroups, the MYOGEN Consortium has recently used genetic data to characterize HLA associations within serology-defined subgroups [91]. For DM specific autoantibody anti-TIF1-γ ($n = 197$), the strongest HLA allele association reaching study-wide significance ($p < 2.9 \times 10^{-5}$) is to HLA-DQB1*02 ($p = 2.34 \times 10^{-11}$, OR 2.49, CI 1.88–3.31). When the cohort is stratified into adult and juvenile-onset patients, anti-TIF1-γ DM ($n = 91$) shows association to HLA-DQB1*02:02 ($p = 2.96 \times 10^{-5}$), whereas anti-TIF1-γ JDM ($n = 106$) shows association to HLA-DQB1*02:01 ($p = 3.70 \times 10^{-5}$), part of the 8.1 ancestral haplotype. These different genetic associations in adult and juvenile-onset anti-TIF1-γ positive patients may indicate different underlying etiology. For the anti-Mi2 subgroup ($n = 104$), the strongest association is to HLA-DRB1*07:01 ($p = 4.92 \times 10^{-13}$, OR 5.47, CI 3.48–8.77), with trends in the same direction for both adult- and juvenile-onset. For anti-SAE ($n = 31$), significant association was observed to HLA-DQB1 amino acid position 57 (omnibus $p = 2.66 \times 10^{-6}$), but not to any classical HLA alleles. DM-specific autoantibodies anti-NXP2 ($n = 93$) and anti-MDA5 ($n = 35$) did not show any association reaching study-wide significance. Altogether, these data demonstrate that DM autoantibody subgroups have different HLA allele and amino acid associations, and that these associations may be stronger than for clinically defined subgroups.

Dr. Yves Allenbach discussed mechanisms of myofiber injury in DM. He discussed the fact that myopathological analysis shows that (i) muscle fibers are atrophic, (ii) atrophic fibers are clustered in perifascicular areas and (iii) myofibers have evidence of mitochondrial damage [92].

The other pathological feature involves the vascular domain with a vasculopathy characterized by the presence of perivascular inflammatory infiltrates, capillary loss, endothelial complement deposits and undulating tubules within the endothelial cells (electronic microscopy).

The interferon (IFN) pathway plays a key role in both muscle fibers and vascular injuries. The IFN levels and IFN signature scores are increased in the blood of DM and are correlated with the disease activity [93]. In muscle tissues IFN stimulated genes are upregulated, especially in the perifascicular areas [62,94]. IFN related proteins are also detected in muscle fibers in perifascicular areas and their detection is now considered to be a potential DM diagnostic biomarker [63,95]. In vitro studies showed that IFN impairs myoblast differentiation and induces myotubes atrophy [96,97]. Finally, IFN also induces mitochondrial dysfunction, mediated by ROS, contributing to poor exercise capacity [93].

The observation that some inherited interferonopathies, characterized by defective regulation of IFN, have a severe vasculopathy (stimulator of IFN genes-associated vasculopathy with onset in infancy: SAVI) [98] strongly suggests the pathological role of IFN on endothelial cells. In DM muscle samples there is a correlation between the vascular damage and the IFN levels [99] and there is also a correlation between IFN stimulated genes or IFN related proteins with related angiogenesis genes and proteins [97]. In vitro, IFN impairs endothelial cell angiogenesis [97]. Together these data highlight the IFN pathogenic role on the vascular compartment.

Muscle injury may be also induced by hypoxia. A clue regarding this mechanism can be found in the case of livedoid vasculopathy, a very rare condition characterized by a thrombo-occlusive vasculopathy of superficial dermal micro-vessels (purpura, livedo and ulcerations) due to thrombophilia. This condition may also affect the muscle when it causes a severe vasculopathy leading to perifascicular myofiber damage [100]. This observation suggests that the

perifascicular region is especially sensitive to ischemic insult. In addition, in vitro hypoxia induces IFN-related protein expression and IFN secretion by myotubes [101]. Taken together, these findings suggest a key role for IFN in the pathophysiology of DM. Accordingly, recent clinical data suggest that IFN-pathway inhibition using Janus-Kinase inhibitors may improve refractory DM patients [97].

Dr. Manabu Fujimoto next gave an overview of animal models of myositis. Although no animal models of DM have been established, there are many animal models of autoimmune myositis. The classical murine model is well known as experimental autoimmune myositis (EAM) [102]. EAM is induced by immunizations of muscle homogenate or partially purified myosin with complete Freund's adjuvant (CFA). However, the only susceptible strain is the SJL mouse that has a mutant *Dysferlin* gene. Therefore, improved models have been reported. Allenbach and colleagues reported a highly reproducible EAM model in Balb/c or C57BL/6 mice that were immunized repeatedly once a week for 3 weeks with 1 mg purified myosin with CFA [103]. Kohsaka and colleagues also reported that immunization of skeletal C-protein, a myosin-binding major immunogenic protein in the myosin fraction induced myositis in C57Bl/6 mice (C protein-induced myositis; CIM) [104]. This CIM model is inducible in B6 mice. Nonetheless, CIM is characterized by CD8 T cells-mediated muscle fiber-injury, suggesting that CIM is more representative of PM than DM. Moreover, these proteins are different from antigens targeted by myositis-specific autoantibodies in human myositis.

As for antisynthetase syndrome, mice immunized with the Jo-1 antigen, histidyl-tRNA synthetase, have been reported to develop myositis and lung disease in congenital B6 mice [105]. Also, a recent study by Boyer et al. demonstrated that IgG transfer from IMNM patients with anti-SRP or anti-HMGCR autoantibodies can cause the disease in mice [106]. He concluded that developing experimental DM models related to DM-specific autoantigens, such as TIF1-γ proteins, would be beneficial to investigate the pathogenesis of the human disease.

Dr. Fujimoto also gave an overview on mechanisms of skin damage in DM. Despite the characteristic and distinguishable clinical manifestation, the histopathological findings of cutaneous eruptions are unspecific and similar to those in lupus. For example, liquefaction degeneration of basal keratinocytes, dermal mucin deposition, perivascular mononuclear cell infiltration, and vascular injury are observed to varying degrees. Like lupus, molecular mechanisms of skin damage in DM are likely to be related to type I IFNs as the increased expression of type I IFN-inducible genes have been reported [107,108]. However, considering the clinical heterogeneity across different autoantibody groups, the histopathology would also have to be evaluated based on autoantibody profiles. He presented preliminary data that histopathological features as well as type I IFN-inducible gene expression are distinct for each myositis-specific autoantibody.

6. Juvenile manifestations of DM and inherited interferonopathies

Professor Lucy Wedderburn reviewed the recent advances in juvenile DM, with a focus on so called endotypes of disease, their MSA associations and how they relate to pathological features seen in muscle biopsy tissue. In most large cohorts of juvenile onset myositis, including the UK Juvenile DM Cohort and Biomarker Study (JDCBS) [109] approximately 65% of children have a detectable MSA [110]. The prevalence of the different MSAs differs in childhood onset myositis from adult onset IIM [110,111] with the most common MSAs in JDM cases being TIF1-γ (~20–25%) and NXP2 (18–20%), while Jo-1, MDA-5 and Mi2 MSAs are relatively rare in children. A recent large UK study has suggested that as MSAs are not detectable in JSLE or juvenile arthritis, testing of MSAs might be useful as part of early diagnostic work up [111]; however, as yet, data are lacking on whether MSAs may be found in the monogenic interferonopathies, such as chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) and SAVI syndromes in children, which may be a diagnostic challenge in younger patients.

Clinical associations with some specific MSAs are well documented in JDM. Interestingly age at onset also seems to play a role in such associations, with one clear example being calcinosis which is associated with a positive NXP2 MSA but also closely correlated with age of onset of disease [112]. In contrast the TIF1-γ autoantibody appears to be associated with risk of cancer in adults but not in children and a recent study of the isotype of TIF1-γ autoantibodies in adults and children suggests that the cancer risk may associate with specific isotype of anti-TIF1-γ autoantibodies [87]. A recent genetic analysis also suggests that unlike previous data for other MSAs, the HLA genetic associations for adult and paediatric onset cases of TIF1-γ positive IIM may also differ [113]. Together these data suggest that immune changes with age have differential influences on the specific autoimmune responses to autoantigens in IIM.

The UK group have shown that the MSA data when combined with quantitative histopathological score data measuring severity features on quadriceps muscle biopsy tissue in JDM [25,26] provides prognostic value in predicting disease course and how quickly treatment can be tapered or stopped [24]. In a recent study which included a detailed evaluation of 101 JDM biopsies the UK group has shown that severity of biopsy features is significantly different in different MSA groups with Mi2 positive cases having classic, severe features, MDA-5 positive cases having mild or minimal pathological changes. However, both the anti-TIF1-γ and anti-NXP2 positive groups were heterogeneous in terms of severity and features on biopsy [114]. Interestingly the degree of IFN driven expression of MxA protein in muscle biopsies was also found to be differentially expressed in different MSA groups as well as correlating with weakness as measured by the CMAS clinical score [115].

Dr. Cyril Gitiaux presented on the topic of acquired interferonopathies associated with skin lesions**.** He reminded the audience that juvenile IIMs, including juvenile DM and, less frequently, juvenile overlap myositis, are highly heterogeneous diseases characterized by multiple combinations of clinical, biological and histopathological patterns challenging the need for reliable and minimally invasive biomarkers of short/long-term outcome, disease activity and response to treatment [116]. Juvenile IIMs are mostly viewed as non-Mendelian disorders, with disease susceptibility being linked to the HLA locus as in other autoimmune diseases [89]. A very rare condition, CANDLE, may mimic juvenile DM with early onset, similar cutaneous rash, myositis and calcinosis. This condition is linked to mutations in genes encoding proteasome components, thus leading to proteasome malfunction, disruption of proteostasis and dysregulation of IFN signaling [117]. A working hypothesis is that juvenile DM is associated with a type 1 IFN upregulation triggered by one environmental stimulus, targeting a genetically susceptible child. The upregulation of type 1 IFN is associated with two major pathologic features in muscle tissue: (i) multifocal capillary loss and (ii) perifascicular atrophy. The exact chain of events leading to loss of blood capillaries and to perifascicular atrophy remains unknown. Mendelian type 1 interferonopathies are a paradigm of type1 IFN upregulation and are characterized by disturbance of the homeostatic control of these IFN-mediated immune responses. They are usually present in early life and may mimic congenital infection or be mistaken for sporadic autoimmune diseases such as SLE or JDM [118]. Most particularly, SAVI, due to TMEM173 gain of function (GOF) mutation, can demonstrate severe ILD and skin vasculitis reminiscent of MDA5+ JDM phenotype [98]. However, muscle involvement has not been described so far as a prominent feature in the Mendelian type 1 interferonopathies.

Biological research conducted mainly in JDM have demonstrated that type1 IFN upregulation plays an important role in the immunopathogenesis of JDM [119–121]. The type 1 IFN (IFN-I) signature is detectable in muscle fibers, myogenic precursor cells (MPCs), and muscle endothelial cells. Transcriptomic analysis performed in myoblasts isolated from JDM muscles showed a strong IFN-I signature. Endothelial cells in JDM muscle downregulate genes related to vessel development, cell adhesion and migration, which are essential for angiogenesis. Downregulation of these genes, in addition to the production of angiostatic cytokines/chemokines, are likely key events in the development of the vasculopathy seen in juvenile DM. Furthermore, juvenile DM-derived MPCs displayed an efficient pro-angiogenic activity that triggered capillary elongation and lumenization. IFN-I triggered pro-angiogenic signature and properties in normal MPCs in vitro, suggesting an IFN-I pathway through which MPCs may stimulate vascular remodeling and trigger muscle recovery in JDM [99]. An increased level of interferon-stimulated gene (ISG) expression in peripheral blood and IFNα measurement by digital ELISA, even at very low concentrations, are useful for diagnostic screening for juvenile myositis and may allow therapeutic stratification and/or monitoring of therapeutic responses [120]. Treatments targeting the IFN pathway are beginning to be used in small numbers of patients with interferonopathies. In particular, the JAK inhibitors are emerging as a potentially important therapeutic strategy for JDM [122].

7. Treatment in DM

Professor Ingrid Lundberg reminded attendees that there have been very few controlled trials in patients with IIMs in general and that in DM, there are no consensus-based treatment guidelines or recommendations. Thus, available treatment recommendations are mainly based on case series and expert opinion.

As a general principle for treatment of patients with DM, pharmacological treatment should be combined with exercise as proposed by Oddis and Aggarwal in a recent review on treatment of DM and PM [123]. The authors propose an algorithm for pharmacological treatment with glucocorticoids in combination with either methotrexate or azathioprine as first-line therapy. As second-line therapy, mycophenolate mofetil (MMF), tacrolimus or ciclosporin, or combination therapy such as azathioprine and methotrexate may be considered. Third-line therapies include rituximab, cyclophosphamide, repository corticotropin injection (RCI) or other experimental biologic agents. Intravenous immunoglobulin (IVIG) can be used alone as a first-line, second-line or third-line therapy or as a concomitant therapy with any drug depending on clinical phenotype and comorbidities.

More specifically treatment recommendations for patients with DM should include use of sunscreens and local therapies including topical steroids, intralesional steroids or topical tacrolimus. In one of the few controlled trials in DM, three months of treatment with high dose IVIG was superior to placebo concerning improvement of muscle strength according to the MRC scale and a neuromuscular symptom score [124]. Also, the skin rash improved in 8 patients. However, this was a small study including only 15 patients with refractory DM and, although convincing data, the results have not yet been replicated.

Concerning biological treatment, a post-hoc analysis of the rituximab in myositis (RIM) trial, a placebo-controlled trial in PM and DM, demonstrated improvement of the skin score with a change in skin activity in a VAS Score from 3.20 ± 2.46 to 1.72 ± 2.09 [125]. Furthermore, the frequency of any DM rash decreased from 89% (64/72) to 76% (51/67) ($p = 0.047$) after 36 weeks.

In a randomized placebo-controlled pilot study in DM, prednisone was combined with etanercept or placebo and then followed by a forced prednisone taper [126]. At the end of the 24-week trial, the average daily prednisone dose in the etanercept arm was 1.2 mg whereas it was 29.2 mg in the placebo arm. None of the patients in the placebo group ($n = 5$) managed to stop steroid treatment after 24 weeks, whereas

5/11 patients in the etanercept arm could be weaned off prednisone suggesting a steroid-sparing effect of etanercept. These findings need to be confirmed in a larger trial.

The only FDA approved drug for myositis, repository corticotropin injection (RCI), H.P. Actar gel, was recently demonstrated to have beneficial effect on disease activity in refractory PM and DM patients in a small 24-week pilot study. Among the patients with significant DM-related skin rash, 4 of 5 improved in the cutaneous VAS score of the Myositis Disease Activity Assessment Tool (MDAAT) by 88% [127].

Although there are some promising data on pharmacological treatment effects in patients with DM [97], large controlled trials are clearly needed. Furthermore, some patients are still resistant to available treatment; therefore, new therapies are needed and increased knowledge about molecular disease mechanisms will be important.

Dr. Victoria Werth next presented on skin outcome measures for DM trials. She discussed the need for independent critical evaluation of skin manifestations of DM with reliable and validated measure of skin disease severity. This requires a precise outcome measure that is reliable, consistent with high inter- and intra-rater reliability, that also has validity and sensitivity. DM clinical trials and patient-focused evidence-based medicine requires such a validated disease severity tool.

The cutaneous DM disease area and severity index (CDASI) was developed to systematically assess the extent of cutaneous disease in patients with DM and to allow for capturing responsiveness. Content validity was developed through discussion with investigators, clinicians, and patients. Construct validity was evaluated by demonstrating agreement between the CDASI and the cutaneous assessment tool (CAT) [128]. There were iterative changes in the instrument based on these discussions, leading to a second slightly simpler version2 that performed as well as the initial CDASI [129]. The goal was an instrument that was quick to use, had high inter-rater and intra-rater reliability, and would describe a few clear signs that allowed grading of disease severity. Damage and activity were scored separately to avoid the paradoxical stability of a combined score, where activity can decrease as damage increases. The disease attributes are scored in 15 anatomic sites in terms of the degree of erythema, scale, and erosions/ulceration. Damage is evaluated by the presence of poikiloderma, defined as dyspigmentation or telangiectasias, and calcinosis. The worst area for each attribute in a given body area is scored, as determining the predominant color or other characteristic for an area can often be difficult, and% area is even more difficult. Gottron's sign/papules, hair loss, and proximal nailfold changes are scored separately.

Next to the CDASI there are two other skin outcome measures developed for DM, the CAT [130,131], and the Dermatomyositis Skin Severity Index (DSSI). The CDASI and CAT have been compared in several validation studies, and the CDASI has higher inter-rater and intra-rater reliability on formal testing, as well as lower SRM values [128,132]. The CAT requires the skin findings to totally resolve in order to capture change, making it hard to capture meaningful change in the context of a trial. The DSSI is based on body surface area. Since DM can be on small surface areas, like the hands, but cause significant activity in these smaller locations, the DSSI does not capture the important changes.

The CDASI is able to capture nuanced, but important, changes in the skin, and there is a linear correlation between CDASI activity and patient's quality of life (QoL), as measured by the Skindex [133]. In addition, a meaningful change in CDASI based on the patients meaningful change in QoL (MCID) has been defined [134], and studies based on even smaller changes in CDASI have demonstrated meaningful improvement in QoL, including itch and pain [135]. Previous studies based on the change in the physician visual analogue scale (VAS) determined a meaningful improvement from a clinical perspective as a five-point change in CDASI [136]. Using the patient perspective to determine meaningful change from a QoL perspective, for those with a threshold CDASI-A score range of >14, a 40% change or delta decrease in CDASI of 10 in CDASI-A score is associated with a meaningful change in QoL [134].

Validation of the CDASI has been extended to adult and pediatric rheumatologists, while neurologists had more variation and thus lower inter-rater reliability [137,138]. The CDASI is a reliable instrument for use by dermatologists and rheumatologists that are trained in its use, while the data is not as robust for neurologists.

CDASI activity correlates with a number of blood and skin biomarkers. One study showed the serum IFN-β linearly correlated with CDASI activity, and those with a CDASI activity score of ≥ 12 had higher IFN-β serum levels relative to those with mild disease [93]. The change in a 10-gene IFN signature correlated with the change in CDASI.

The CDASI was used as a primary outcome for a phase 2 double-blind placebo-controlled trial of a nonpsychoactive cannabinoid, lenabasum [139]. It was able to demonstrate significant improvement in the skin in a short trial that has now led to a phase 3 global trial. Many patient-reported outcomes correlated with the improvement seen in the CDASI.

Professor Jiří Vencovský next discussed muscle outcome measures for use in clinical trials. He noted that a preliminary core set of disease outcome measures for use in clinical trials in IIMs was proposed in 2001 [140]. The six core set activity domains that were recommended for inclusion in all myositis clinical trials were patientś and physician's global assessment of disease activity, muscle strength, physical function, laboratory evaluation, and assessment of extra-skeletal muscle involvement. The degree of change in each core set measure that is clinically meaningful was defined [141]. Consensus definition of improvement required 3 of any 6 of the core set measures improved by $>20\%$, with no more than 2 worse by $>25\%$ (which could not include manual muscle testing to assess strength) [142]. The criteria were considered preliminary, because they were not prospectively validated. It was acknowledged that these criteria had several limitations, such as equal weight applied to each core set measure, lack of

quantitative or continuous outcome, and ceiling effect in some core set measures. New improvement criteria were released in 2017. They use weighted assessment of core set measures reflecting the importance of contribution of each measure to disease improvement [143,144]. The highest weight is given to improvement in muscle weakness, followed by improvement in global disease activity assessed by physician, extramuscular manifestations, global disease activity by patient, physical function, and muscle enzymes. The latter parameter is weighted least reflecting low association between enzyme level change and clinical improvement in some cases. The criteria provide continuous results and generate a total improvement score (on a scale of 0–100). Change can be also categorized into minimal, moderate and major improvement based on the fulfilment of thresholds. The criteria are recommended to be used in all clinical trials in myositis.

Measurement of muscle weakness or muscle performance is considered the most important for evaluation of patients with myositis. Manual muscle testing (MMT) of proximal muscle groups or a total MMT score involving proximal, distal and axial muscles, as well as abbreviated unilateral MMT of 8 muscle groups (MMT-8) have been preliminary validated using 0–10 MMT scale [145]. The expanded 0–10 scale is thought to enhance the sensitivity of strength testing. MMT-8, which includes neck flexors, deltoids, biceps, wrist extensors, gluteus maximus and medius, quadriceps and ankle dorsiflexors, performed as well as or better than total MMT and is recommended for use in therapeutical trials. MMT-8 takes less time and requires less patient effort than other MMTs and is therefore suitable for longitudinal follow-up.

Another possibility is to test muscle endurance. This is currently done using the functional index 2 (FI-2) [146] in which dynamic repetitive muscle function (DRMF) is tested. Patients perform as many repetitions of each muscle group as they can, or they stop when reaching maximal number of repetitions. A percentage of maximum is calculated for each task and a sum on different muscle groups provides the final scoring. Recently, muscle endurance deficits have been described despite normal manual muscle testing scores [147]. Muscle endurance testing may therefore identify muscle impairment inadequately described by MMT, particularly in patients with high MMT scores [148]. Another recent study showed that patients with adult PM and DM might be more limited in DRMF than in isometric muscle strength, again pointing out the importance of assessing dynamic muscle function in addition to the MMT-8 [149].

An attempt to improve performance in measurement of muscle impairment combines MMT-8 with 3-items of Childhood Myositis Assessment Scale (CMAS) and is thus more comprehensive than the former and more feasible than the latter [150]. The tool (hMC) possesses good measurement properties but needs further testing.

Another, more simple possibility to evaluate muscle activity and its change is the repeated use of the visual analogue scale for muscle disease activity which is part of the MDAAT developed by IMACS [151], in which patients score presence of clinical features or symptoms within the previous 4 weeks that are due to active disease. Similarly, in another IMACS tool, muscle damage is measured based on combined consideration of the presence of muscle atrophy, muscle weakness not attributable to active muscle disease, decrease in aerobic exercise capacity, low serum creatinine, and if available, muscle atrophy assessed by radiographic methods [151].

Recently, there has been a proposal for a candidate core-set of fitness and strength tests for patients with childhood or adult IIMs. It includes treadmill exercise stress test (modified Bruce protocol), incremental cycle ergometer test, 6 min walk test (6MWT), handgrip strength, MMT, CMAS in children, and FI-2 in adults [152].

Laboratory biomarker tool measures serum activities of at least 2 of the 4 muscle-associated enzymes including creatine kinase (CK), the transaminases (ALT, AST), lactate dehydrogenase (LD) and aldolase. The most abnormal serum muscle enzyme value at baseline is used for longitudinal follow up [143].

Isometric dynamometry provides a quantitative measure testing (QMT) that might be sensitive in detecting small changes in strength as well as mild weakness that might not be detected by MMT [153]. There are many different instruments to measure quantitative muscle strength. The person administering the test must be trained. Like other measures of strength, QMT does not discriminate between activity and damage. There is almost no validation in patients with myositis [154].

Hand held dynamometry (HHD) correlation with MMT-8 has not been found satisfactory, suggesting different construct measurement [155]. HHD could be recommended to evaluate isometric muscle strength of single muscle groups in people with myositis if the following important aspects are considered: examiners are experienced and trained in muscle testing, a standardized protocol is followed, a belt to stabilize examiner or the device is used, and the average of at least two measures is applied.

Home accelerometers emerge as new tools to measure muscle performance in patients with myositis [156]. Numerous variables, such as average daily step count and acceleration vector magnitude, can be used to describe the intensity, duration and types of activity. The tool is practical, objective, provides continuous longitudinal monitoring and carries lack of cognitive input from patient or examiner. However, there is a need for standardization and interpretation [154].

Muscle imaging by magnetic resonance (MRI) demonstrates both inflammatory and post-inflammatory changes in the muscles and surrounding soft tissue. In patients with established diagnosis MRI can help to determine whether clinical muscle weakness is based on chronic muscle damage or relapse of active disease [157]. The characteristic MRI findings in patients with DM are high signal intensities in subcutaneous tissue and fascial areas, peripheral distribution and honeycomb pattern [158]. There is no standardized protocol for evaluation of MRI in patients

with myositis. There is a need to define the exact parameters, anatomical localizations, precise MR imaging techniques and a potential to change to be used in the future scoring systems [159].

Dr. Lisa Christopher Stine outlined potential future DM treatment trials. She raised some important issues to consider when thinking about trial design, including whether patients with skin-dominant disease should be combined with muscle-dominant DM patient groups. Similarly, she raised the issue of whether patients with ILD should be excluded from trials. Next, she discussed trial design concepts, including whether a placebo group was always needed or whether a crossover design could be employed in most trials, thus providing all patients with the ability to have exposure to the investigational product. Finally, outcome measures including patient reported outcome measures (PROMs) were reviewed.

For cutaneous disease in DM, possible future options may include subcutaneous immunoglobulin, JAK kinase inhibitors such as tofacitinib or ruxolitinib, or tocilizumab, all in current clinical trials [160]. Additional agents currently being investigated for DM include belimumab targeting BAFF [clinical trials.gov] and PF-06823859, a monoclonal antibody against IFN-β [clinical trials.gov] where the predominant outcome measured is the validated CDASI; however patients with muscle diseases are not excluded and muscle strength is captured throughout the trial. [clinical trials.gov].

The final product discussed was Lenabasum (formerly anabasum), a non-psychoactive endocannabinoid receptor agonist. This product is a first-in-class non-immunosuppressive, synthetic, oral preferential CB2 agonist (targets endogenous CB2 receptors on activated immune cells) that triggers resolution of innate immune responses and reduces cytokine production by peripheral blood mononuclear cells from DM patients. The phase 2 trial was an NIH funded 16-week placebo-controlled, randomized trial for 22 cutaneous-predominant DM to investigate safety, tolerability, and efficacy. [clinicaltrials.gov] Inclusion criteria included a (CDASI) activity score $\geq$ 14, minimal active muscle involvement, failure or intolerance to hydroxychloroquine, and stable DM medications including immunosuppressants. The primary outcomes were the number of participants with treatment emergent adverse events as a measure of safety and tolerability at 16 week and change in CDASI scores from baseline at 12 weeks. Results of the trial were promising with all participants completing the trial. Trial subjects had clinically meaningful improvement in CDASI activity scores with mean reduction $\geq$ 5 points at all visits after 4 weeks. Improvement had statistical significance at end of study that first became apparent after 4 weeks. Lenabasum provided greater improvement than placebo in CDAI damage index, patient-reported global skin disease and overall disease assessments, skin symptoms including photosensitivity and itch, fatigue, sleep, pain interference with activities, pain, and physical function. There were no serious, severe or unexpected adverse events (AEs) related to lenabasum and tolerability of lenabasum was excellent. Further evaluation of this compound in the treatment of DM is now underway in a Phase 3 global trial.

8. Autoantibody detection

Livia Casciola-Rosen discussed assays to detect DM autoantibodies. She presented data summarizing the experience of her lab with these assays, noting that the lab's focus is on the research use of these tests rather than clinical utility. That is, the assays are designed to read out each antibody type with rigorously defined specificity, with the recognition that they are not necessarily readily amenable to clinical implementation. Their assay of choice is immunoprecipitation (IP)-based, because it involves recognition of the full-length, non-denatured form of the antigen. Assays to detect Mi2, SAE1, MDA5, NXP2 and PMScl (noting that this last antibody is not DM-specific) were described and data presented. For these, IP of 35S-methionine-labeled protein generated by in vitro transcription and translation (IVTT) from the relevant full-length human DNA is used as input for the IPs. The IPs are electrophoresed on SDS-PAGE gels and visualized by autoradiography [44,53]. Since they first reported on the use of this assay in 2001 (a report of PMS1 antibodies in myositis patients) [161], the lab has worked with >70 different kinds of IVTT products as input for IPs, with cohort sizes ranging from 2 (original description) to ~900. For anti-TIF1-γ autoantibody detection, the preferred assay involves transient transfection of FLAG-tagged TIF1-γ into cultured cells. The resulting lysates have TIF1-γ overexpressed (~30–50 fold), and are used as input for the IPs, with detection by immunoblotting using commercial antibodies against the FLAG tag or TIF1-γ with similar results [8].

The Johns Hopkins Rheumatology's NIH P30-funded Rheumatic Diseases Research Core Center invested in a EuroIMMUN platform recently and has used this to screen a cohort of 261 well-characterized DM plasma samples (a collaboration with Dave Fiorentino, Stanford University) by line blot (LB) using the myositis panel (16 specificities/strip). Since data using the Rosen lab's assays were available with these samples for the DM specificities, this information was compared for autoantibodies recognizing MDA5, Mi2, SAE1, NXP2, PMScl and TIF1-γ. Of note, anti-Jo1 antibody status was available for all samples using the INOVA ELISA kit, with overall excellent concordance of LB and ELISA data. Where available, a third assay was used to readout autoantibodies (MBL ELISA used for anti-Mi2, -MDA5 and -TIF1-γ autoantibodies). Readouts for autoantibodies against Mi2, SAE1 and MDA5 aligned fairly well amongst all assays. Agreement between IVTT IP and LB data from anti-NXP2 autoantibodies was not as good, and there were significant discrepancies for the anti-PMScl and anti-TIF1-γ autoantibody readouts. Assigning correct TIF1γ antibody status is of high importance, given its frequency amongst DM patients and its association with cancer. IVTT IP detected substantially more anti-TIF1-γ-positive samples than the LB assay (41% vs. 15%). It is noteworthy that the third assay

used to test for anti-TIF1-γ autoantibodies (MBL ELISA) detected the same additional samples that IVTT IP read out as being positive, as well as several extra samples, to give 50% positivity for these antibodies in the cohort.

Data presented in this talk highlighted the urgent need for standard adoption of carefully validated platforms to detect these antibodies. Incorrect/missed antibodies affect the clinical phenotyping correlations that are made in cohort studies of these antibodies. This, in turn, impacts clinical utility and relevance for making an accurate diagnosis.

Dr. Jan Damoiseaux presented next on standardization of autoantibody detection methods. He noted that a standard preparation to maximize compatibility and enabling uniformity of measuring results of autoantibody testing for autoimmune diseases is a major challenge. The underlying problem is the high variability in the composition of the autoantibody repertoire within and between individuals. As a consequence, samples may react differently in distinct immunoassays. Most international initiatives on the preparation of standards utilize plasmapheresis material from a single patient. By definition, this is never representative for the whole patient population and, partly because of this, the ultimate goal of standardization has not yet been met.

Harmonization, i.e., the adjustment of differences among measurements, methods, and procedures by recommendations and/or guidelines to improve compatibility, might be the highest achievable goal. Harmonization can be obtained at several levels of autoantibody testing. First of all, requesting of the autoantibody tests by the clinician can be guided by well-defined clinical manifestations. Such a gating-strategy prevents testing of patients with a low pre-test probability and, as a consequence, a relatively high rate of false-positive results (i.e., low specificity). Second, the laboratory specialist has to choose the most optimal testing system/algorithm. In case of DM, immunoprecipitation is considered the gold standard method. However, immunoprecipitation is not a standard method and is not readily available in most routine diagnostic laboratories. Alternative immunoassays, like line- or dot-immunoassays, are limited in the availability of appropriate clinical evaluations [162]. Although it is evident that the HEp-2 indirect immunofluorescent test (IIFT) is not an optimal screening test for IIMs, the HEp-2 IIFT pattern could be used to support the identified antigen-specificity of the DM-specific autoantibody [163]. The third level of harmonization involves the way test-results are being reported by the laboratory specialist to the clinician. For some DM-specific autoantibodies there exist two antigenic entities: Mi2α and Mi2β, and SAE-1 vs. SAE-2. Evidently, test characteristics will differ for both entities and, therefore, it should be specified to which antigen(s) the autoantibodies are reactive. Low-, medium-, and high-positive results will also have distinct test characteristics and this can best be underscored by reporting in likelihood ratios for test-result intervals [164]. Fourth, the test-results obtained should be interpreted by the clinician in the context of the clinical manifestations of the patients. In particular if test-results are reported as likelihood ratios and if pre-test probabilities are available for the clinical manifestations defined for autoantibody testing, the post-test probabilities can be calculated based on Bayes' theorem.

Altogether, it should be anticipated that standardization of autoantibody testing is not a realistic goal for the very near future. Harmonization, on the other hand, can be achieved by implementing recommendations/guidelines at several levels. Considering that DM is a relatively rare disease, such harmonization requires a collaborative effort to define a gating strategy and to obtain the relevant data, like reliable test-characteristics and pre-test probabilities.

9. DM, rashes, and the antisynthetase syndrome

Dr. Victoria Werth opened this session by discussing the features that define a DM rash. She noted that the Bohan and Peter criteria defined DM for many years [165,166]. These criteria did not allow recognition of amyopathic DM patients, since patients had to have some muscle abnormalities to be recognized as even possible DM. Sontheimer's criteria for the skin findings of DM include pathognomonic findings of Gottron's papules and Gottron's sign. Characteristic findings include heliotrope, periungual telangiectasias, dystrophic cuticles, and photodistributed violaceous erythema. Secondary skin features of DM include subepidermal vesicle and/or blisters which could evolve into superficial erosion/ulcerations. Other secondary features include vasculopathy, poikiloderma (hyperpigmentation and hypopigmentation, telangiectasias, and superficial atrophy), as well as cutaneous calcinosis. The International Myositis Classification Criteria Project (IMCCP) utilized a collaborative and scientific approach to develop criteria that would allow recognition of amyopathic DM, with three skin criteria determined as important to include as criteria: heliotrope, Gottron's papules, and Gottron's sign. The presence of two of the three skin variables allowed recognition of patients as having DM [2,3,167]. A skin biopsy showing typical changes of interface dermatitis was included as part of the selection criteria for subjects used in the criteria study, and it was recommended to utilize skin biopsies in addition to the clinical criteria to avoid inclusion of mimickers of DM. These new EULAR/ACR criteria allow classifying amyopathic DM in approximately 75% of patients [168].

There is now an ongoing collaborative effort to further refine the skin variables, so that more CADM patients can be correctly classified as DM. A pre-delphi, followed by two rounds of Delphi have narrowed potential classification criteria from 54 to 22 items that are now being tested prospectively in an international collaboration including dermatologists and rheumatologists. The variables to be tested include morphology, distribution, symptoms, presence of myositis antibodies, and contextual factors such as interstitial lung disease (ILD) and muscle weakness. The goal is to develop and validate skin criteria for DM so as to correctly classify as many patients as possible, with the target group being patients with amyopathic DM.

Features of DM can be helpful in terms of determining risk of ILD, with mechanics hands seen somewhat more often in patients with ILD, although prevalent in those without ILD or antisynthetase antibodies [169]. It is clear that antisynthetase antibodies can be seen in patients with skin features of DM, and thus defining DM with or without antisynthetase antibodies may help define distinct subsets. Many patients with DM or CADM and ILD do not have antisynthetase antibodies, so there is a lot of overlap of systemic features. MDA-5 antibodies define a subset of patients who may have rapidly progressive ILD. MDA-5 patients have more lung disease, skin ulcers, palmar papules, mechanics hands, oral lesions, and alopecia [44]. Skin ulcers in DM can be due to vasculopathy, vasculitis, excessive inflammation at the interface between the dermis and epidermis, or due to excoriations in response to pruritus. Antibodies are beginning to help define phenotypes of disease. There is however, a need for better standardization of measurement of DM autoantibodies. A recent study showed just 14% of patients with DM had MSAs and 21% had MSAs when testing was done in commercial labs [170]. Hopefully the detection rate of autoantibodies will improve with time and allow better correlation with disease phenotype.

To summarize, Dr. Werth noted that clinical findings in the skin include both primary and secondary changes. The new EULAR/ACR criteria allow identifying 75% of patients with amyopathic DM. An ongoing prospective study will further refine criteria for the patients with skin predominant disease. Histology in about 80% of cases of DM show interface dermatitis. There are some cases that don't show that pattern and that can make the diagnosis more difficult. The key is clinical and pathological correlation.

Next, Dr. Marianne de Visser discussed the significance of DM-like features in antisynthetase syndrome, and whether patients with aminoacyl transfer RNA synthetase (ARS) autoantibodies and a rash should be considered to have DM.

The typical clinical findings of antisynthetase syndrome (arthritis, myositis, and interstitial lung disease [defined as classic triad manifestations]) are found in only 20% of patients at the onset of the disease, reaching more than 50% throughout follow-up [171]. Noguchi et al. [172] described the dermatological findings in 51 patients with antisynthetase syndrome. Mechanics hands were seen in 16 patients (31%), although Gottron's sign/papules and heliotrope rash which are considered characteristic of DM were also reported (Gottron, 14 [27%]; heliotrope, 7 [14%]; both, 3 [6%]) in patients with different ARS antibodies. Conversely, mechanic hands can also be observed in DM. Ang et al. [169] reported that 3 out of 3 DM patients with anti-MDA5 antibodies and 12 out of 17 DM subjects with anti-TIF1-γ had mechanic's hands.

As regards the histology, muscle biopsies taken from antisynthetase syndrome patients show similarities with DM, including necrotic and regenerating fibers scattered throughout the muscle biopsy specimen, perimysial perivascular mononuclear cell infiltrates and alkaline phosphatase positivity of the perimysial connective tissue [172,173], but there are also differences, i.e., necrotic muscle fibers located in the perifascicular region are found in about half of the antisynthetase syndrome muscle biopsies, whereas in DM there is perifascicular atrophy and sarcoplasmic expression of MxA in a fair proportion of the cases (55% and 77%, respectively) [64].

Based on the above, one might argue that some antisynthetase syndrome patients have much in common with DM and could, in fact, be considered to have a form of DM. However, Olivier Benveniste presented the counter argument, first recalling that the initial description of anti-Jo1 autoantibodies in 1980 was made in a series of 8 out of 26 PM patients (31%) and only 1 out of 22 DM patients [174]. The first series of antisynthetase syndrome cases in 1990 described PM (not DM), ILD, and autoantibodies to aminoacyl-tRNA synthetase enzymes [175]. Furthermore, in a recently published multiple correspondence analysis with unsupervised hierarchical cluster analysis [176], professor Benveniste and colleagues described 4 subgroups of patients: IBM, IMNM, DM and antisynthetase syndrome. Importantly, DM and antisynthetase syndrome were clearly separated in this unsupervised analysis. By using the former Bohan and Peter classification criteria [177,178], they observed that 95% of antisynthetase patients are in the PM subgroup and only 5% were classified DM. He also noted that although Gottron rash/papules can sometimes be observed in patients with ASA, the skin biopsy from these patients do not stain positive for MxA as they do in DM (as discussed by Dr. Fujimoto).

Muscle pathology is also different between antisynthetase syndrome and DM even if perifascicular atrophy can be observed in both conditions. In contrast to DM, antisynthetase syndrome muscle biopsies are characterized by perifascicular necrosis, perimysial fragmentation [67], HLA DR staining of the perifasciculum [66], absence of MxA upregulation [64] and nuclear abnormalities with actin inclusions [179]. Finally, the IFN signatures are also different between DM and antisynthetase syndrome, with type I being prominent in DM and type II predominant in antisynthetase syndrome.

In summary, Professor Benveniste noted that differences in each dimension (i.e., phenotype, MSA, skin pathology, muscle pathology, and physiopathogenesis) strongly indicate that antisynthetase syndrome is a unique subgroup among the different forms of myositis, including DM.

10. Do DM-specific autoantibodies define distinct subtypes of DM?

Next, Professor Ingrid Lundberg summarized data presented at the meeting bearing on the question of whether the different DM-specific autoantibodies should be used to define distinct DM subtypes. She reviewed the detailed presentations given on clinical and histopathological features of muscle and skin associated with the anti-TIF1-γ, anti-NXP2, anti-Mi2, anti-MDA5 and ant-SAE autoantibodies. The group agreed that these data strongly suggest that different autoantibody specificities are associated with different clinical phenotypes. For example, anti-TIF1-γ and anti-NXP2 autoantibodies are associated with malignancies

Table 1
ENMC 2018 dermatomyositis classification criteria.

1. A DM classification can be made if the following clinical and skin biopsy features are present*:
   (a) Clinical exam findings (at least two of the following): Gottron's sign, Gottron's papules, and/or heliotrope rash.
   (b) Skin biopsy findings: interface dermatitis.
2. A DM classification can be made if the following clinical features are present along with either DM muscle features** or a DM-specific autoantibody***:
   (a) Clinical exam findings (at least one of the following): Gottron's sign, Gottron's papules, and/or heliotrope rash.

*Based on established skin criteria that allow classification of clinically amyopathic DM [2,3].

**DM muscle features
1. Proximal muscle weakness.
2. Elevated muscle enzymes.
3. Suggestive DM muscle biopsy findings: lymphocytic infiltrates (often perivascular), evidence of perifascicular disease (perifascicular predominant fibers that are pale on COX staining and/or positive on NCAM staining).
4. Definitive DM muscle biopsy findings: perifascicular atrophy and/or perifascicular MxA overexpression with rare or absent perifascicular necrosis.

The DM muscle features requirement is met if patients have: (a) 1 and 2, (b) 1 and 3, (c) 2 and 3, or (d) 4.

***DM-specific autoantibodies
1. Anti-TIF1γ
2. Anti-NXP2
3. Anti-Mi2
4. Anti-MDA5
5. Anti-SAE

Additional notes
- A classification of DM cannot be made in the absence of cutaneous DM features.
- Patients with an antisynthetase autoantibody will be classified as having the antisynthetase syndrome and not DM. Antisynthetase syndrome patients with a DM-like rash will be classified as having "the antisynthetase syndrome with a DM-like rash".
- Patients with anti-HMGCR or anti-SRP autoantibodies will be classified as having IMNM and not DM. Anti-HMGCR+ patients with a DM-like rash will be classified as having "anti-HMGCR myopathy with a DM-like rash". Anti-SRP+ patients with a DM-like rash will be classified as having "anti-SRP myopathy with a DM-like rash".
- Patients with a DM-specific autoantibody will be subclassified according to that autoantibody (e.g., anti-TIF1γ DM, anti-NXP2 DM, etc.…)
- Patients who have DM without a DM-specific autoantibody will be subclassified as having "autoantibody negative DM".
- Ulcerating lesions on the extensor surfaces of the metacarpophalangeal, proximal interphalangeal, and/or distal interphalangeal joints (as may be seen in anti-MDA5 DM) are considered equivalent to Gottron's papules.

whereas anti-MDA5 autoantibodies are associated with RP-ILD, which is rarely found in anti-TIF1-γ- or anti-NXP2-positive patients [180]. Different skin features, distributions and severity of skin rash vary between these five MSA subgroups. Likewise, data show that anti-MDA5 and anti-SAE autoantibodies are often associated with mild muscle weakness or amyopathic DM whereas patients with anti-Mi2 antibodies often have severe muscle weakness.

In addition, histopathological features in skin and muscle are different between patients with different MSAs. For example, as presented by Professor Stenzel, muscle biopsies from patients with anti-Mi2 antibodies typically display perimysial connective tissue changes with fragmentation and alkaline phosphatase activity and biopsies from patients with anti-TIF1-γ autoantibodies often display perifascicular changes and MAC depositions on capillaries [68]. Of note, MxA staining was also different among subsets of DM patients defined by different autoantibodies [64].

In summary, accumulating clinical and histopathological data suggest that different pathophysiological mechanisms may be involved in patients with different DM autoantibodies leading to different types of skin rash and muscle pathology. Differences in immune mechanisms are further supported by associations of different MSAs with different HLA types [91].

Importantly, in most laboratories, about 25% of patients with DM test negative for currently identified autoantibodies; the clinical and histopathological features of these patients require further study. Moreover, whether these patients might have novel autoantibodies still needs to be addressed.

11. Reaching consensus

The group reached consensus about how to classify patients with DM (Table 1). The proposed new classification system recognizes that DM autoantibodies are specific for DM and they now have an important role in the classification scheme. Furthermore, the group reached consensus that DM is not a homogeneous entity. Rather, each DM autoantibody is associated with a distinctive clinical phenotype (Table 2) and DM autoantibodies can be used to define 6 different subtypes of DM: (1) anti-TIF1-γ DM, (2) anti-NXP2 DM, (3) anti-Mi2 DM, (4) anti-MDA5 DM, (5) anti-SAE DM, and (6) autoantibody negative DM.

There was some lively discussion about whether the rare patient with a DM autoantibody, muscle weakness, and a muscle biopsy showing perifascicular atrophy, but who does not have a rash, should be diagnosed with DM. Ultimately, in our newly proposed classification scheme, cutaneous DM features, but not muscle involvement, is required for a patient to be classified as DM.

Importantly, patients with antisynthetase autoantibodies are considered to have a separate disease, the antisynthetase

Table 2
Clinical features associated with each dermatomyositis autoantibody in adults.

	Anti-Mi2	Anti-TIF1γ	Anti-NXP2	Anti-MDA5	Anti-SAE
Prevalence among DM	5–20%	15–25%	15–25%	5–20%	~5%
Muscle					
Severity of weakness	+++	+	++	+	+
Pattern of weakness	Proximal	Proximal	Proximal/distal	Proximal	Proximal
CK levels (mean peak)	+++	++	+++	+	+
Biopsy features					
Perifascicular atrophy	++	++	++	+	?
Skin					
Gottron's/heliotrope	++	+++	++	++	?
Ulcerations	–/+	–/+	+	+++	?
Calcinosis	–/+	–/+	++	–/+	?
Interstitial lung disease	–/+	–/+	–/+	+++	+
Cancer risk	?	+++	++	+	?

syndrome, and are not considered to be within the DM myositis type even if they have typical DM-skin involvement. Similarly, patients with anti-HMGCR or anti-SRP autoantibodies, even if they have rashes, are considered to have IMNM and should not be classified as having DM.

The group agreed that each DM subtype has different clinical features and that each is likely to have different underlying disease mechanisms. Therefore, future DM clinical trials should give consideration to either (a) only including DM patients with a particular defined autoantibody or (b) stratifying patients by autoantibody status. As antisynthetase patients have a distinct type of disease, even antisynthetase patients with a rash should not be included in DM clinical trials.

Finally, and importantly, the proposed classification criteria for DM and its autoantibody-associated subgroups from this ENMC workshop need to be validated in clinical cohorts. Ideally, this validation effort would occur as part of a multicenter collaboration including a large number of patients with different clinical profiles to allow comparisons between different subgroups. Eventually, with longitudinal follow up, time will tell if these subgroups vary in treatment response and prognosis.

12. Workshop participants

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Acknowledgments

This Workshop was made possible thanks to the financial support of the European Neuromuscular Centre (ENMC) and ENMC main sponsors:

- Association Française contre les Myopathies (France)
- Deutsche Gesellschaft für Muskelkranke (Germany)
- Muscular Dystrophy Campaign (UK)
- Muskelsvindfonden (Denmark)
- Prinses Beatrix Spierfonds (The Netherlands)
- Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (Switzerland)
- Telethon Foundation (Italy)
- Spierziekten Nederland (The Netherlands) and Associated members:
- Finnish Neuromuscular Association (Finland)
- Österreichische Muskelforschung (Austria)

With a special thanks to members of the ENMC Company Forum

- Sanofi Genzyme
- Santhera Pharmaceuticals
- Amicus Therapeutics
- CSL Behring LLC
- Ionis Pharmaceuticals
- Perkin Elmer/Wallac Oy
- AveXis Switzerland GmbH
- Biogen International GmbH
- Hoffmann-la-Roche
- Sanquin Plasma Products

This research was also supported by the Intramural Research Programs of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS; ZIA AR041203).

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