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Review

Strategy for suspected myositis

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ABSTRACT

Skeletal muscle inflammation is the feature shared by all forms of myositis. However, the muscle damage ranges in severity from asymptomatic to responsible for severe weakness. In addition, myositis usually occurs as a systemic disease that affects multiple organs. More specifically myositis should be considered in patients with muscular, cutaneous, pulmonary, and articular manifestations. The definitive diagnosis and classification of myositis has benefited considerably in recent years from the identification of characteristic autoantibodies. Nonetheless, a muscle biopsy is often necessary to confirm the diagnosis, and the differential diagnoses may raise challenges that require evaluation at a myositis referral center. The management depends on the type of myositis. Treatments should be provided for both the systemic complications (involving the lungs, heart, gastrointestinal tract, and/or joints) and the comorbidities (cancer and risks factors for cardiovascular disease, thromboembolism, and fractures), which together determine the prognosis. Many drugs are available for treating myositis. Findings from randomized controlled trials will help to use them optimally.

1. When to suspect myositis

Skeletal muscle inflammation is a feature shared by all types of myositis. The severity of the muscle damage induced by the inflammation varies widely, and patients may be asymptomatic or present with severe muscle weakness. In addition, myositis usually occurs as a systemic diseases that affects multiple organs. Thus, the clinical scenarios that should suggest myositis cover a broad spectrum.

1.1. Muscle symptoms suggestive of myositis

1.1.1. Muscle weakness

In current diagnostic criteria sets, including the recent ACR/EULAR criteria [1], muscle weakness is the only item used to assess muscle function impairment. Difficulty standing from a low seat, Gowers' sign, and/or downward drifting of one or both arms during sustained forward elevation (Barré's test) indicate substantial muscle weakness. When the muscle damage is less severe, manual muscle testing is required to detect the weakness. Factors that may influence muscle testing results include muscle strength before disease onset, the substantial inter-observer variability of muscle strength testing results, and a threshold effect.

1.1.2. Loss of muscle endurance and decrease in physical activity

Several muscle parameters that are not considered in current diagnostic criteria sets are affected more severely than muscle strength. Examples are muscle endurance [2] and amount of movement as measured using actimetry [3]. For clinical research, the Functional Index-2 (FI-2) is used to assess muscle endurance and accelerometry to quantify movement. In everyday practice, both parameters can be easily and rapidly evaluated by asking about any changes in walking distance or physical activities and by using clinical tests such as timed counts of stands from a squatting or seated position and timed sustained forward arm elevation (Barré's test) or leg elevation with 90° hip and knee flexion in the supine position (Mingazzini's test).

1.1.3. Muscle wasting

Muscle wasting may be the most prominent manifestation, notably in slowly progressive myositis subtypes such as sporadic inclusion body myositis and certain forms of necrotizing autoimmune myopathy. Severe muscle wasting can mistakenly suggest an inheritable myopathy [4] or sarcopenia [5]. Furthermore, a

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diagnostic pitfall in patients with advanced myositis responsible for muscle loss is that the creatine kinase (CK) levels may be normal.

1.1.4. Muscle pain

Myalgia, although a common reason for seeking medical advice about the possibility of myositis, has very low specificity. Thus, in addition to myositis, many other diseases are associated with myalgia, including endocrinopathies, connective tissue diseases, vascular diseases, radiculopathies, osteoarticular diseases, and fibromyalgia. Furthermore, a study in the general population found that 10% of individuals reported myalgia [6].

Similarly, the absence of myalgia does not rule out myositis. On the contrary, muscle pain is usually absent in necrotizing autoimmune myopathy, although this form of myositis induces severe muscle weakness, serum CK elevation, and muscle lesions visible by magnetic resonance imaging (MRI) and histology [7].

1.1.5. Serum creatine kinase (CK) elevation

Serum CK elevation is among the items used in current diagnostic criteria sets for myositis, including the set developed recently by the ACR/EULAR [1]. The serum CK level correlates with the amount of necrotic muscle [8]. Consequently, the CK level may be normal in forms of myositis characterized by limited necrosis (e.g., inclusion body myositis and dermatomyositis [9]) and in patients whose muscle mass is small. Thus, in a patient with other evidence suggestive of myositis, a CK level at the upper limit of normal does not rule out the diagnosis.

CK levels above the normal range indicated by the laboratory should be interpreted according to age and sex if no other signs are present. Among healthy volunteers, over one-third had CK levels above the normal range [10]. Laboratories should provide normal ranges adjusted for patient sex and geographic origin [11] (Table 1).

1.2. Joint symptoms suggestive of myositis

The joint manifestations of myositis consist of inflammatory arthralgia or arthritis symmetrically involving the small joints. The presentation may mimic rheumatoid arthritis, and tests for anti-citrullinated peptide antibodies (ACPAs) may be positive or negative.

Although not among diagnostic criteria, joint involvement is present in about half the patients with myositis. A higher prevalence of up to 90% has been reported in patients with overlap myositis syndromes (antisynthetase syndrome [12], scleromyositis [13], mixed connective tissue disease), or anti-MDA5 dermatomyositis [14,15]. Isolated joint symptoms have been reported to be inaugural in up to 30% of patients with antisynthetase syndrome [16].

In patients with symmetrical inflammation of the small joints, the following three signs should be sought to avoid missing a diagnosis of myositis: muscle manifestations as described above; radiological findings of interstitial lung disease, notably nonspecific interstitial pneumonia (as opposed to usual interstitial pneumonia, as seen in rheumatoid arthritis); and positive cytoplasmic immunofluorescence on Hep-2 cells. These signs can be easily assessed using inexpensive tests. The presence of one or more of them should prompt additional investigations for myositis, including a test for ACPA, which is typically negative in myositis.

1.3. Lung symptoms suggestive of myositis

Nonspecific interstitial pneumonia is the most common lung manifestation of myositis. Other forms of lung disease such as usual interstitial pneumonia, bronchiolitis obliterans organizing pneumonia, and diffuse alveolar damage or mixed CT patterns can occur also [17]. Similar to joint symptoms, lung symptoms are not included in diagnostic criteria sets, despite being found in 20% to 78% of patients [18] and occurring as the inaugural isolated symptom in some cases [12].

In a recent study, patients who had interstitial pneumonia with autoimmune features but did not meet criteria for a definite connective tissue disease often had autoantibodies associated with myositis, such as antisynthetase antibodies (up to 35%), anti-RNP (up to 15%), and anti-PM/SCL (up to 5%). Although the commercially available assays for these antibodies are not 100% specific [19,20], these data suggest that subclinical myositis may sometimes be present at the diagnosis of interstitial pneumonia with autoimmune features. In keeping with this possibility, syndromes associated with antisynthetase and anti-PM/Scl antibodies are often incomplete initially [12,13]. Diagnosing myositis has major implications, since earlier treatment of the lung disease probably improves patient outcomes [21].

Interstitial lung disease is both uncommon and life-threatening, and diagnosing myositis has major therapeutic implications. Consequently, patients with respiratory symptoms should probably undergo, not only a CK assay, but also extensive tests for antibodies associated with myositis and interstitial lung disease, even when Hep-2 immunofluorescence is negative.

1.4. Cutaneous symptoms suggesting myositis

The skin manifestations of dermatomyositis have the highest weight among clinical items in the ACR/EULAR criteria for myositis. They consist of a heliotrope rash of the eyelids and of Gottron's papules and/or macules over the dorsum of the hand joints and extensor aspects of the elbows and knees. These manifestations may be present in patients with mild or no muscle symptoms (hypomyopathic or amyopathic dermatomyositis). Other skin lesions characteristic of dermatomyositis may be present. An example is the reverse Gottron's sign consisting in papules with an ivory-colored center that develop on the palms and are associated with anti-MDA5 antibodies [22]. Psoriasis-like lesions related to anti-TIF1γ have also been reported [23].

Hyperkeratosis with fissuring of the tips and sides of the digits at the hands (mechanic's hand) and/or feet (hiker's feet), although not among the diagnostic criteria for myositis, should be considered suggestive. This manifestation was initially described in association with antisynthetase syndrome and subsequently reported in anti-MDA5-positive dermatomyositis [22] anti-PM/Scl-positive scleromyositis [24].

2. Confirming the diagnosis of myositis

2.1. Autoantibodies

The only autoantibodies among the ACR/EULAR diagnostic criteria are anti-Jo1 (Table 2), although about 20 other autoantibodies have been found helpful for the diagnosis and classification of myositis. The diagnostic criteria developed by Targoff et al. also consider anti-SRP and anti-Mi2 and perform better than do the ACR/EULAR criteria [15] (Table 3 and 4). Classification systems that rely chiefly on autoantibodies have been suggested [25]. Autoantibody tests must be interpreted in the light of the clinical setting, as none is 100% sensitive or specific [20].

2.2. Muscle biopsy

Several experts believe that a muscle biopsy is unnecessary in patients with extra-muscular manifestations (notably skin lesions typical for dermatomyositis) and a positive assay for a myositis-specific autoantibody. Nevertheless, even in the event of dermatomyositis, performing a muscle biopsy improves diagnostic

Table 1
Creatine kinase (CK) cutoffs recommended by the European Federation of Neurological Societies for diagnosing pauci- or asymptomatic hyperCKemia [11]. These cutoffs are based on CK levels measured in a sample of the general population [10].

	Females not from Africa	Males not from Africa	Females from Africa	Males from Africa
97.5th percentile (% general population)	217 IU/L 2.5%	336 IU/L 2.5%	414 IU/L 2.5%	801 IU/L 2.5%
> 1.5–97.5th percentile (% general population)	> 325 IU/L 1.5%	> 504 IU/L 1.0%	> 621 IU/L 1.3%	> 1201 IU/L 0.5%

Table 2
ACR/EULAR criteria with their weights for the diagnosis of myositis (see also Table 4).

	Criteria	Score with muscle biopsy	Score without muscle biopsy
Age at onset	≥ 18 years < 40 years	1.3	1.5
	≥ 40 years	2.1	2.2
Muscle weakness	Roots of upper limbs	0.7	0.7
	Root of lower limbs	0.8	0.5
	Neck flexors > extensors	1.9	1.6
	Lower limbs: proximal > distal	0.9	1.2
Skin	Heliotrope rash	3.1	3.2
	Gottron's papules	2.1	2.7
	Gottron's sign	3.3	3.7
Other	Dysphagia	0.7	0.6
Laboratory tests	Muscle enzymes	1.3	1.4
	Anti-Jo1	3.9	3.8
Muscle biopsy	Endomysial infiltrate		1.7
	Perimysial/perivascular infiltrate		1.2
	Perifascicular atrophy		1.9
	Rimmed vacuoles		3.1

Table 3
: Targoff criteria for diagnosing myositis.

Criteria	
1	Bilateral proximal muscle weakness[a]
2	Muscle enzyme elevation
3	EMG: myogenic muscle unit action potentials, fibrillation potentials, positive sharp waves, increased insertional activity
4	Muscle biopsy: inflammatory infiltrate or necrosis/regeneration or perifascicular atrophy
5	Autoantibodies: anti-synthetase, anti-Mi2, anti-SRP
6	Dermatomyositis skin manifestations: Gottron's sign, Gottron's papules, heliotrope rash

These criteria can be used only after ruling out muscle disease due to infection, toxic agents, metabolic disorders, dystrophy, or endocrine disease.
Criterion 1 or 2 can be replaced by muscle edema.
The results are interpreted as follows: 2 criteria, possible myositis; 3 criteria, probable myositis; and 4 criteria, definite myositis.
[a] Except in inclusion body myositis, in which the weakness is more marked at the finger flexors compared to the shoulder abductors and at the lower-limb extensors compared to the hip flexors.

performance [1]. In other situations, the muscle biopsy is key to the diagnosis of myositis [26,27].

The muscle biopsy should be done at a myositis referral center to ensure optimal diagnostic performance. The sample must be sufficiently large, snap-frozen in isopentane, and processed using about 10 different stains [28]. Considerable experience is needed to interpret the findings. Importantly, inflammatory infiltrates are seen not only in myositis, but also in some of the inheritable myopathies. Furthermore, absence of an inflammatory infiltrate, far from ruling out myositis, is a characteristic feature of necrotizing autoimmune myopathy [29].

In addition to assisting in the diagnosis, the muscle biopsy helps to determine the type of myositis and may supply prognostic information [30].

2.3. Electroneuromyography (ENMG)

ENMG findings are not part of the ACR/EULAR criteria for myositis, although they were included in several earlier criteria sets [1]. The diagnostic yield of ENMG is low in patients with severe myolysis, which strongly supports muscle disease as the cause of weakness. When myolysis is moderate, however, ENMG should be performed to rule out motoneuron disease and diseases affecting the neuromuscular junction (e.g., myasthenia and Lambert-Eaton syndrome), in which moderate myolysis can occur.

2.4. Muscle imaging

MRI, ultrasonography, positron-emission tomography (PET), and computed tomography (CT) are noninvasive tools that can be used to investigate the skeletal muscle. Nevertheless, the findings from these imaging studies are not among the recent ACR/EULAR diagnostic criteria for myositis [1]. They are not specific of myositis but are also seen in many neuromuscular diseases [31]. When other investigations have provided a definitive diagnosis of myositis, however, these imaging studies can help to classify the disease [32,33] and to assess both disease activity and the amount of tissue damage [34,35].

Table 4
Diagnostic performance of the ACR/EULAR, Targoff, and Bohan & Peter criteria for the diagnosis of myositis.

Criteria	Cutoff for the diagnosis	Muscle biopsy	Score	Sensitivity	Specificity
ACR/EULAR	≥ 55%	Yes	5.5	87%	82%
		No	6.7	93%	88%
Bohan & Peter				98%	55%
Targoff				93%	89%

Table 5
Main features of the myositis subgroups.

Myositis subgroup	Distribution of the muscle weakness	Cutaneous manifestations	Specific antibodies (identifiable using commercially available kits)	Specific muscle biopsy findings	Complications that affect the outcome and must be sought
Dermatomyositis	Upper limbs	Dermatomyositis lesions	Anti- Mi-2, -MDA5, -NXP2, -TIF1γ, -SAE	Perifascicular fiber atrophy	Cancer Interstitial lung disease
Necrotizing autoimmune myopathy	Lower limbs (psoas)	None	-SRP, -HMGCR	Randomly distributed fiber necrosis	Cancer (except if anti-SRP) Swallowing disorders
Scleromyositis	Upper limbs	Sclerotic skin, sausage digits	Anti-Scl70, -centromere, -RNAPolII, -PM/Scl, -Ku	Unclear	Interstitial lung disease Pulmonary arterial hypertension Renal crisis
Sharp's syndrome	Unclear	Sausage digits	Anti-U1-RNP	Unclear	Pulmonary arterial hypertension Neurological disorders Renal disorders
Antisynthetase syndrome	Lower limbs (psoas)	Mechanic's hand	-tRNA synthetase (-Jo-1, -PL7, -PL12, -EJ, -OJ, -Ha, -Zo, -Ks)	Perifascicular fiber necrosis	Interstitial lung disease Pulmonary arterial hypertension
Sporadic inclusion body myositis	Flexor digitorum profundis Quadriceps	None	-cN1A (low specificity)	Fibers containing rimmed vacuoles and abnormal protein plaques	Swallowing disorders

2.5. Ruling out differential diagnoses

2.5.1. Other peripheral neuromuscular diseases

In patients with peripheral motor loss, peripheral neuropathies and neuromuscular junction disorders must be ruled out. Moderate myolysis and abnormal muscle imaging findings may occur in these conditions. Marked myolysis should prompt investigations for a cause of myopathy. The muscle biopsy may show an inflammatory infiltrate in patients with inheritable myopathies.

2.5.2. Non-autoimmune interstitial lung disease

Many factors can cause interstitial lung disease, such as medications, infections, environmental exposures, and genetic abnormalities. Investigations must therefore be performed to rule out these causes.

2.5.3. Other inflammatory rheumatic diseases

Other inflammatory rheumatic diseases may mimic myositis if they are responsible for muscle pain, MRI evidence of muscle edema [36], or extra-muscular manifestations also seen in myositis (e.g., interstitial lung disease and Raynaud's phenomenon).

2.5.4. Cutaneous manifestations

Mechanic's hand can be mistaken for digital pulpitis due to irritants or allergies. A heliotrope rash of the eyelids may suggest far more common conditions such as contact dermatitis, atopic dermatitis, seborrheic dermatitis, and rosacea. Gottron's papules and macules may resemble psoriasis. Finally, photo-induced erythema may be confused with lupus.

2.6. Confirming the diagnosis of myositis

Development of the ACR/EULAR criteria set has benefited the diagnosis of myositis. Nevertheless, these criteria can be challenging to use and were designed, not for diagnosis, but to constitute uniform patient groups for inclusion into clinical studies. It is worth noting that the criteria developed by Targoff are easy to use and have performed slightly better than the ACR/EULAR criteria (Tables 2 and 4).

3. Classifying myositis

Simple criteria are effective in separating patients with myositis into subgroups that have different clinical phenotypes and outcomes. Recognition of the subgroup to which a patient belongs is crucial to guide the choice of investigations and treatments. Although no consensus exists at present regarding the classification of myositis [1,25,37], the different classification systems overlap to some extent. These classifications and their rationales were reviewed in a recent article [15]. The main myositis subgroups are shown in Table 5.

3.1. Dermatomyositis

Dermatomyositis is defined by the presence of skin manifestations typical for the disease. Patients with dermatomyositis should be carefully evaluated for cancer, which is associated with anti-TIF1γ and anti-NXP2 autoantibodies, and for lung disease, which is associated with anti-MDA5 antibodies.

3.2. Sporadic inclusion body myositis

Sporadic inclusion body myositis is defined by involvement of the finger flexors and quadriceps and by distinctive histological features including an endomysial infiltrate invading the muscle fibers, which contain rimmed vacuoles and plaques of proteins normally degraded by autophagy.

3.3. Necrotizing autoimmune myopathy

The defining features of necrotizing autoimmune myopathy include biopsy findings of muscle fiber necrosis with deposition of membrane attack complex and scant or absent lymphocytes. Anti-SRP and anti-HMGCR antibodies are associated with this disease [26]. Several characteristics distinguish necrotizing autoimmune myopathy from other types of myositis, such as severe myopathy predominating in the lower limbs contrasting with rare and moderate extra-muscular manifestations. The high risk of cancer in patients with negative tests for autoantibodies must be borne in mind [38].

3.4. Overlap myositis

The prognosis of overlap myositis is dictated by the extramuscular manifestations.

Antisynthetase syndrome is defined by the presence of antisynthetase antibodies [37]. The ACR/EULAR criteria that are being developed will provide a clearer picture of this disease. The currently available antibody assay kits may fail to detect the antisynthetase antibodies (seronegative forms) or produce false-positive results, raising major diagnostic challenges. The risk of interstitial lung disease, pulmonary arterial hypertension [39,40], and joint erosions must receive careful attention [16,41].

Myositis with evidence of scleroderma (scleromyositis) remains ill-defined. The diagnosis is easily established in patients who meet ACR/EULAR criteria for scleroderma. However, most of the patients who produce scleroderma-associated antibodies that are not among the ACR/EULAR criteria (anti-Ku [42], anti-PM/Scl [13]) do not meet these criteria. Importantly, patients with scleromyositis are at risk for interstitial lung disease, pulmonary arterial hypertension, cardiac involvement, and scleroderma renal crisis.

Sharp's syndrome is characterized by anti-U1-RNP antibodies. Myositis associated with Sharp's syndrome may be associated with pulmonary arterial hypertension, neurological disease, and nephropathy [43,44].

4. Assessing the extent of myositis

A broad range of complications may develop. The type of myositis guides the choice of the investigations performed to detect them.

4.1. Investigations for cancer

About 20% of adults with myositis have cancer [45], which is among the three leading causes of death in patients with myositis [46]. Risk factors for cancer are older age, male sex, and severe cutaneous manifestations of dermatomyositis, whereas joint and/or lung involvement are associated with a lower risk of cancer [45]. In patients with dermatomyositis, anti-TIF1γ production is a risk factor for cancer [47], although the association may be weaker when highly sensitive assays are used to detect these antibodies [48]. The presence of anti-NXP2 [48] and anti-SAE [49] may also be a risk factor for cancer. Necrotizing autoimmune myopathy is more likely to be a paraneoplastic disease when tests are negative for known antibodies and, to a lesser degree, when they are positive for anti-HMGCR antibodies [38].

For patients with dermatomyositis, the European Federation of Neurological Societies recommends performing the following investigations once a year for 3 years: CT of the chest, abdomen, and pelvis in all patients; colonoscopy in all patients older than 50 years; pelvic ultrasonography and mammography in females older than 50 years; and ultrasonography of the testes in males older than 50 years [50]. French recommendations include performing upper gastrointestinal tract endoscopy and colonoscopy in patients who have necrotic skin lesions and/or anti-TIF1γ and/or anti-NXP2 antibodies [51]. There is no convincing evidence to date that PET-CT improves the diagnostic yield compared to the standard workup.

4.2. Detection and evaluation of lung involvement

Lung disease is one of the three leading causes of mortality among patients with myositis [46]. Patients who have respiratory symptoms or risk factors for lung disease (anti-MDA5, anti-synthetase, anti-Ku, anti-PM/Scl, anti-RNP, anti-Scl70, and/or anti-centromere antibodies) should undergo chest imaging and lung function testing including measurement of the transfer factor of the lung for carbon monoxide.

4.3. Investigations for cardiac involvement

Cardiovascular complications are among the three main causes of death in patients with myositis [46]. They are related to the inflammatory process and to atherosclerosis. In addition, myositis is associated with venous thromboembolic events, a detailed below.

Cardiac involvement can be detected by electrocardiography and by echocardiography of the right and left chambers. A troponin I assay may help to detect cardiac involvement, and troponin I levels correlate with the activity of the skeletal muscle involvement [52].

4.4. Investigations for gastrointestinal involvement

Impaired swallowing and dysphagia have been reported in 10% to 80% of patients with myositis. When these symptoms are severe, they are associated with a higher risk of death, usually due to aspiration pneumonia [53]. They are most common in inclusion body myositis [50], scleromyositis [51], paraneoplastic dermatomyositis [52], and necrotizing autoimmune myopathy [53]. Asking the patient about symptoms and measuring the time needed to swallow a glass of water are sufficient to detect impaired swallowing and dysphagia.

4.5. Investigations for joint involvement

Joint involvement is a major source of pain and disability. Patients should be asked specifically about joint symptoms. Radiographs of symptomatic joints should be obtained given the risk of bone and joint destruction [41].

5. Detecting and preventing comorbidities

The comorbidities associated with myositis make a major contribution to morbidity and mortality [46]. They are related both to the myositis and to the treatments.

5.1. Evaluating and controlling the cardiovascular risk

Adults with myositis are at increased risk for myocardial infarction (risk ratio ≈4) and for ischemic and hemorrhagic vascular events (risk ratio ≈2), particularly during the first year after the diagnosis [54,55]. A recent study of an inpatient care database in the US showed an increased risk of cardiovascular and cerebrovascular events in children with dermatomyositis [56].

At the diagnosis of myositis, investigations should be performed to detect cardiovascular risk factors, and prophylactic measures should be implemented. Statin therapy is contraindicated only in patients with anti-HMGCR antibodies.

5.2. Evaluating and controlling the risk of venous thromboembolism

Compared to the general population, patients with myositis have an about 7-fold increase in the risk of venous thromboembolism, and the risk is greatest within 1 year after the diagnosis [57]. Thromboembolism prophylaxis should be initiated at the time of the diagnosis of myositis. The modalities and nature of the prophylactic treatment vary according to the risk of bleeding and to the risk factors for thrombosis, notably those directly related to the disease (weakness, inflammatory syndrome, and cancer).

5.3. Evaluating and controlling the risk of infection

Risk factors for infection include age, joint manifestations, and lung disease [58]. In addition, immunosuppression increases the risk of opportunistic infection [59]. An immunization strategy similar to that recommended by the ACR/EULAR for rheumatoid arthritis may be applied [60]. The appropriateness of *Pneumocystis jirovecii* prophylaxis should be assessed.

5.4. Evaluating and controlling the risk of fracture

The high glucocorticoid dosages used to treat myositis are associated with bone loss, and recommendations for assessing and mitigating the fracture risk should therefore be followed. A study of a national health insurance database in Taiwan found a 3-fold increase in the risk of osteoporosis among patients with myositis [61]. In a cross-sectional study, about half the patients with myositis had asymptomatic vertebral fractures and about a quarter of patients whose bone mineral density was measured had osteoporosis [62]. Both greater disease activity and a higher cumulative glucocorticoid dose were associated with bone loss [63].

6. Treatments for myositis

Randomized controlled trials of treatments in myositis are scarce, and obtaining advice from a myositis referral center is therefore desirable. Except in patients with inclusion body myositis, immunomodulating therapy should be initiated promptly. The treatment modalities depend on disease severity, the extent of the manifestations, and the type of myositis. An exercise program should be recommended in addition to the drug therapy [64].

Glucocorticoids (1 mg/kg/d per os, or bolus injections if required by disease severity) are still used as induction therapy despite the absence of randomized controlled trials designed to assess the benefits of this strategy. Furthermore, a treatment approach that did not include glucocorticoids proved effective in statin-induced anti-HMGCR-positive myositis [65].

Methotrexate and azathioprine have been associated with improved patients outcomes [66–68]. The better safety profile of methotrexate may warrant a preference for this drug for the first-line treatment, as recommended for pediatric patients with dermatomyositis [69]. Methotrexate is not contraindicated in patients with mild interstitial lung disease.

Mycophenolate mofetil, calcineurin antagonists, and cyclophosphamide are second-line drugs [70]. Data from case-series studies suggest that they may be effective against myositis-related interstitial pneumonia, and they should therefore be given preference when respiratory manifestations are at the forefront of the clinical picture [71].

Immunoglobulins have been proven beneficial in patients with refractory dermatomyositis [72] and are also used to treat other types of refractory myositis [26,73]. The first-line use of immunoglobulins in patients with dysphagia or severe muscle weakness has been suggested [51].

Rituximab was not more effective than a placebo after 3 months [74]. After 44 months, in contrast, improvements were noted in 83% of rituximab-treated patients with refractory myositis. Other data indicate that rituximab may improve myositis-related lung disease [75] and experts have recommended rituximab therapy in patients with severe interstitial pneumonia [71,76]

Promising results have been reported with other biotherapies (abatacept [77], anakinra [78], and tocilizumab [79]).

The interferon I signature associated with dermatomyositis and the muscle toxicity of interferon I [9] recently prompted the use of janus kinase inhibitors (JAK 1/2 and JAK 1/3), since one effect of these drugs consists in blockade of the interferon I pathway [80,81]. The improvements noted in the cutaneous, muscular, and pulmonary manifestations of myositis noted with these drugs warrant a randomized controlled trial.

No treatments have been found effective in inclusion body myositis. Methotrexate decreased the serum CK levels but failed to slow the decline in muscle strength [82]. In a preliminary randomized placebo-controlled trial, rapamycin failed to affect muscle weakness progression but slowed the decrease in 6-minute walking distance, the deterioration of a weakness index, and the progression of fatty muscle infiltration [83].

7. Conclusion

Myositis should be considered in patients with muscular, cutaneous, pulmonary, and/or joint manifestations. The identification in recent years of autoantibodies associated with myositis has produced substantial diagnostic benefits. Nevertheless, a muscle biopsy remains required in many patients. The management strategy varies with the type of myositis. The systemic manifestations of myositis and comorbidities govern the prognosis and should therefore receive careful attention.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Lundberg IE, Tjärnlund A, Bottai M, et al. European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Ann Rheum Dis 2017;76:1955–64.
[2] Amici DR, Pinal-Fernandez I, Pagkatipunan R, et al. Muscle endurance deficits in myositis patients despite normal manual muscle testing scores. Muscle Nerve 2018, http://dx.doi.org/10.1002/mus.26307.
[3] Bachasson D, Landon-Cardinal O, Benveniste O, et al. Physical activity monitoring: a promising outcome measure in idiopathic inflammatory myopathies. Neurology 2017;89:101–3.
[4] Suzuki S, Hayashi YK, Kuwana M, et al. Myopathy associated with antibodies to signal recognition particle: disease progression and neurological outcome. Arch Neurol 2012;69:728–32.
[5] Needham M, Corbett A, Day T, et al. Prevalence of sporadic inclusion body myositis and factors contributing to delayed diagnosis. J Clin Neurosci Off J Neurosurg Soc Australas 2008;15:1350–3.
[6] Kissel JT. Muscle biopsy in patients with myalgia: still a painful decision. Neurology 2007;68:170–1.
[7] Watanabe Y, Uruha A, Suzuki S, et al. Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. J Neurol Neurosurg Psychiatry 2016;87:1038–44.
[8] Allenbach Y, Arouche-Delaperche L, Preusse C, et al. Necrosis in anti-SRP+ and anti-HMGCR+myopathies: role of autoantibodies and complement. Neurology 2018;90:e507–17.
[9] Meyer A, Laverny G, Allenbach Y, et al. IFN-β-induced reactive oxygen species and mitochondrial damage contribute to muscle impairment and inflammation maintenance in dermatomyositis. Acta Neuropathol (Berl) 2017;134:655–66.
[10] Brewster LM, Mairuhu G, Sturk A, et al. Distribution of creatine kinase in the general population: implications for statin therapy. Am Heart J 2007;154:655–61.
[11] Kyriakides T, Angelini C, Schaefer J, et al. EFNS guidelines on the diagnostic approach to pauci- or asymptomatic hyperCKemia. Eur J Neurol 2010;17:767–73.
[12] Cavagna L, Nuño L, Scirè CA, et al. Clinical spectrum time course in anti Jo-1 positive antisynthetase syndrome: results from an international retrospective multicenter study. Medicine (Baltimore) 2015;94:e1144.
[13] De Lorenzo R, Pinal-Fernandez I, Huang W, et al. Muscular and extramuscular clinical features of patients with anti-PM/Scl autoantibodies. Neurology 2018;90:e2068–76.
[14] Goussot R, Theulin A, Goetz J, et al. An arthro-dermato-pulmonary syndrome associated with anti-MDA5 antibodies. Joint Bone Spine 2014;81:266.
[15] Meyer A, Lannes B, Goetz J, et al. Inflammatory myopathies: a new landscape. - PubMed - NCBI. Joint Bone Spine 2018;85:23–33.
[16] Lefèvre G, Meyer A, Launay D, et al. Seronegative polyarthritis revealing antisynthetase syndrome: a multicentre study of 40 patients. Rheumatol Oxf Engl 2015;54:927–32.
[17] Kiely PDW, Chua F. Interstitial lung disease in inflammatory myopathies: clinical phenotypes and prognosis. Curr Rheumatol Rep 2013;15:359.

[18] Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. BMJ 2016;352:h6819.
[19] Sambataro G, Sambataro D, Torrisi SE, et al. State of the art in interstitial pneumonia with autoimmune features: a systematic review on retrospective studies and suggestions for further advances. Eur Respir Rev Off J Eur Respir Soc 2018, http://dx.doi.org/10.1183/16000617.0139-2017.
[20] Cavazzana I, Fredi M, Ceribelli A, et al. Testing for myositis specific autoantibodies: Comparison between line blot and immunoprecipitation assays in 57 myositis sera. J Immunol Methods 2016;433:1–5.
[21] Kurita T, Yasuda S, Oba K, et al. The efficacy of tacrolimus in patients with interstitial lung diseases complicated with polymyositis or dermatomyositis. Rheumatol Oxf Engl 2015;54:1536.
[22] Fiorentino D, Chung L, Zwerner J, et al. The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study. J Am Acad Dermatol 2011;65:25–34.
[23] Fiorentino DF, Kuo K, Chung L, et al. Distinctive cutaneous and systemic features associated with antitranscriptional intermediary factor-1γ antibodies in adults with dermatomyositis. J Am Acad Dermatol 2015;72:449–55.
[24] Marie I, Lahaxe L, Benveniste O, et al. Long-term outcome of patients with polymyositis/ dermatomyositis and anti-PM-Scl antibody. Br J Dermatol 2010;162:337–44.
[25] Senécal J-L, Raynauld J-P, Troyanov Y. Editorial: A New Classification of Adult Autoimmune Myositis. Arthritis Rheumatol 2017;69:878–84.
[26] Allenbach Y, Mammen AL, Benveniste O, et al. 224th ENMC International Workshop: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016. Neuromuscul Disord NMD 2018;28:87–99.
[27] Lloyd TE, Mammen AL, Amato AA, et al. Evaluation and construction of diagnostic criteria for inclusion body myositis. Neurology 2014;83:426–33.
[28] Dubowitz V, Sewry C, Oldfors A. Histological and histochemical stains and reactions. Muscle Biopsy: A Pract Approach 2007:21–39, http://dx.doi.org/10.1016/B978-1-4160-2593-1.50007-3.
[29] Hilton-Jones D. Myositis mimics: how to recognize them. Curr Opin Rheumatol 2014;26:663–70.
[30] Aouizerate J, De Antonio M, Bader-Meunier B, et al. Muscle ischaemia associated with NXP2 autoantibodies: a severe subtype of juvenile dermatomyositis. Rheumatology 2018;57:873–9.
[31] May DA, Disler DG, Jones EA, et al. Abnormal signal intensity in skeletal muscle at MR imaging: patterns, pearls, and pitfalls. Radiogr Rev Publ Radiol Soc N Am Inc 2000;20:S295–315.
[32] Cox FM, Reijnierse M, Rijswijk V, et al. Magnetic resonance imaging of skeletal muscles in sporadic inclusion body myositis. Rheumatology 2011;50:1153–61.
[33] Yoshida K, Nishioka M, Matsushima S, et al. Brief report: Power Doppler ultrasonography for detection of increased vascularity in the fascia: A potential early diagnostic tool in fasciitis of dermatomyositis: PDUS for detection of dermatomyositis-associated fasciitis. Arthritis Rheumatol 2016;68:2986–91.
[34] Pinal-Fernandez I, Casal-Dominguez M, Carrino JA, et al. Thigh muscle MRI in immune-mediated necrotising myopathy: extensive oedema, early muscle damage and role of anti-SRP autoantibodies as a marker of severity. Ann Rheum Dis 2017;76:681–7.
[35] Malattia C, Damasio MB, Madeo A, et al. Whole-body MRI in the assessment of disease activity in juvenile dermatomyositis. Ann Rheum Dis 2014;73:1083–90.
[36] Meyer A, Lannes B, Garnon J, et al. Muscle MRI: All that glitters is not myositis. Joint Bone Spine 2016;83:349.
[37] Mariampillai K, Granger B, Amelin D, et al. Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies. JAMA Neurol 2018, http://dx.doi.org/10.1001/jamaneurol.2018.2598.
[38] Allenbach Y, Keraen J, Bouvier A-M, et al. High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. Brain J Neurol 2016;139:2131–5.
[39] Hervier B, Meyer A, Dieval C, et al. Pulmonary hypertension in antisynthetase syndrome: prevalence, aetiology and survival. Eur Respir J 2013;42:1271–82.
[40] Hervier B, Devilliers H, Stanciu R, et al. Hierarchical cluster and survival analyses of antisynthetase syndrome: phenotype and outcome are correlated with anti-tRNA synthetase antibody specificity. Autoimmun Rev 2012;12:210–7.
[41] Meyer A, Lefevre G, Bierry G, et al. In antisynthetase syndrome, ACPA are associated with severe and erosive arthritis: an overlapping rheumatoid arthritis and antisynthetase syndrome. Medicine (Baltimore) 2015;94:e523.
[42] Hoa S, Hudson M, Troyanov Y, et al. Single-specificity anti-Ku antibodies in an international cohort of 2140 systemic sclerosis subjects: clinical associations. Medicine (Baltimore) 2016;95:e4713.
[43] Coppo P, Clauvel JP, Bengoufa D, et al. Inflammatory myositis associated with anti-U1-small nuclear ribonucleoprotein antibodies: a subset of myositis associated with a favourable outcome. Rheumatol Oxf Engl 2002;41:1040–6.
[44] Lundberg I, Nyman U, Pettersson I, et al. Clinical manifestations and anti-(U1)snRNP antibodies: a prospective study of 29 anti-RNP antibody positive patients. Br J Rheumatol 1992;31:811–7.
[45] Wang J, Guo G, Chen G, et al. Meta-analysis of the association of dermatomyositis and polymyositis with cancer. Br J Dermatol 2013;169:838–47.
[46] Dobloug GC, Svensson J, Lundberg IE, et al. Mortality in idiopathic inflammatory myopathy: results from a Swedish nationwide population-based cohort study. Ann Rheum Dis 2018;77:40–7.
[47] Trallero-Araguás E, Rodrigo-Pendás JÁ, Selva-O'Callaghan A, et al. Usefulness of anti-p155 autoantibody for diagnosing cancer-associated dermatomyositis: a systematic review and meta-analysis. Arthritis Rheum 2012;64:523–32.
[48] Fiorentino DF, Chung LS, Christopher-Stine L, et al. Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1γ. Arthritis Rheum 2013;65:2954–62.
[49] Muro Y, Sugiura K, Nara M, et al. High incidence of cancer in anti-small ubiquitin-like modifier activating enzyme antibody-positive dermatomyositis. Rheumatol Oxf Engl 2015;54:1745–7.
[50] Titulaer MJ, Soffietti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur J Neurol 2011;18:e19–23.
[51] Bader-Meunier B, Benveniste O. Dermatomyosite de l'enfant et de l'adulte; 2016. p. 110.
[52] Lilleker JB, Diederichsen ACP, Jacobsen S, et al. Using serum troponins to screen for cardiac involvement and assess disease activity in the idiopathic inflammatory myopathies. Rheumatol Oxf Engl 2018;57:1041–6.
[53] Oh TH, Brumfield KA, Hoskin TL, et al. Dysphagia in inflammatory myopathy: clinical characteristics, treatment strategies, and outcome in 62 patients. Mayo Clin Proc 2007;82:441–7.
[54] Rai SK, Choi HK, Sayre EC, et al. Risk of myocardial infarction and ischaemic stroke in adults with polymyositis and dermatomyositis: a general population-based study. Rheumatol Oxf Engl 2016;55:461–9.
[55] Svensson J, Lundberg IE, Von Euler M, et al. The risk of ischemic and haemorrhagic stroke in idiopathic inflammatory myopathies: a Swedish population-based cohort study. Arthritis Care Res 2018, http://dx.doi.org/10.1002/acr.23702.
[56] Silverberg JI, Kwa L, Kwa MC. Cardiovascular and cerebrovascular comorbidities of juvenile dermatomyositis in US children: an analysis of the National Inpatient Sample. Rheumatol Oxf Engl 2018;57:694–702.
[57] Carruthers EC, Choi HK, Sayre EC, et al. Risk of deep venous thrombosis and pulmonary embolism in individuals with polymyositis and dermatomyositis: a general population-based study. Ann Rheum Dis 2016;75:110–6.
[58] Chen I-J, Tsai W-P, Wu Y-JJ, et al. Infections in polymyositis and dermatomyositis: analysis of 192 cases. Rheumatol Oxf Engl 2010;49:2429–37.
[59] Redondo-Benito A, Curran A, Villar-Gomez A, et al. Opportunistic infections in patients with idiopathic inflammatory myopathies. Int J Rheum Dis 2018;21:487–96.
[60] Singh JA, Saag KG, Bridges SL, et al. 2015 American college of rheumatology guideline for the treatment of rheumatoid arthritis: ACR RA treatment recommendations. Arthritis Care Res 2016;68:1–25.
[61] CW-S Lee, Muo C-H, Liang J-A, Sung F-C, Hsu C-Y, Kao C-H. Increased osteoporosis risk in dermatomyositis or polymyositis independent of the treatments: a population-based cohort study with propensity score. Endocrine 2016;52:86–92.
[62] Gupta L, Lawrence A, Edavalath S, Misra R. Prevalence and predictors of asymptomatic vertebral fractures in inflammatory myositis. Int J Rheum Dis 2018;21:725–31.
[63] So H, Yip ML, Wong AKM. Prevalence and associated factors of reduced bone mineral density in patients with idiopathic inflammatory myopathies. Int J Rheum Dis 2016;19:521–8.
[64] Alexanderson H, Lundberg IE. Exercise as a therapeutic modality in patients with idiopathic inflammatory myopathies. Curr Opin Rheumatol 2012;24:201–7.
[65] Mammen AL, Tiniakou E. Intravenous immune globulin for statin-triggered autoimmune myopathy. N Engl J Med 2015;373:1680–2.
[66] Ruperto N, Pistorio A, Oliveira S, et al. Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial. Lancet Lond Engl 2016;387:671–8.
[67] Schiopu E, Phillips K, MacDonald PM, et al. Predictors of survival in a cohort of patients with polymyositis and dermatomyositis: effect of corticosteroids, methotrexate and azathioprine. Arthritis Res Ther 2012;14:R22.
[68] Yu K-H, Wu Y-JJ, Kuo C-F, et al. Survival analysis of patients with dermatomyositis and polymyositis: analysis of 192 Chinese cases. Clin Rheumatol 2011;30:1595–601.
[69] Enders FB, Bader-Meunier B, Baildam E, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. Ann Rheum Dis 2017;76:329–40.
[70] Oddis CV, Aggarwal R. Treatment in myositis. Nat Rev Rheumatol 2018;14:279–89.
[71] Morisset J, Johnson C, Rich E. Management of Myositis-Related Interstitial Lung Disease. Chest 2016;150:1118–28.
[72] Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med 1993;329:1993–2000.
[73] Cherin P, Pelletier S, Teixeira A, et al. Results and long-term followup of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients. Arthritis Rheum 2002;46:467–74.
[74] Oddis CV, Reed AM, Aggarwal R, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum 2013;65:314–24.
[75] Andersson H, Sem M, Lund MB, et al. Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease. Rheumatol Oxf Engl 2015;54:1420–8.
[76] Cavagna L, Monti S, Caporali R, et al. How I treat idiopathic patients with inflammatory myopathies in the clinical practice. Autoimmun Rev 2017;16:999–1007.

[77] Tjärnlund A, Tang Q, Wick C, et al. Abatacept in the treatment of adult dermatomyositis and polymyositis: a randomised, phase IIb treatment delayed-start trial. Ann Rheum Dis 2018;77:55–62.
[78] Zong M, Malmström V, Lundberg IE. Anakinra effects on T cells in patients with refractory idiopathic inflammatory myopathies. Ann Rheum Dis 2011;70:A80-1.
[79] Narazaki M, Hagihara K, Shima Y, et al. Therapeutic effect of tocilizumab on two patients with polymyositis. Rheumatol Oxf Engl 2011;50:1344–6.
[80] Ladislau L, Suárez-Calvet X, Toquet S, et al. JAK inhibitor improves type I interferon induced damage: proof of concept in dermatomyositis. Brain J Neurol 2018;141:1609–21.
[81] Kurasawa K, Arai S, Namiki Y, et al. Tofacitinib for refractory interstitial lung diseases in anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis. Rheumatol Oxf Engl 2018, http://dx.doi.org/10.1093/rheumatology/key188.
[82] Badrising UA, Maat-Schieman MLC, Ferrari MD, et al. Comparison of weakness progression in inclusion body myositis during treatment with methotrexate or placebo. Ann Neurol 2002;51:369–72.
[83] Benveniste O, Hogrel J-Y, Annoussamy M, et al. Rapamycin vs. placebo for the treatment of inclusion body myositis: improvement of the 6 min walking distance, a functional scale, the FVC and muscle quantitative MRI. Arthritis Rheumatol 2017;69:5L.