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9

How to investigate: Suspected systemic rheumatic diseases in patients presenting with muscle complaints

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A B S T R A C T

Muscular symptoms, which may be due to multiple causes, are one of the most common early complaints in a rheumatology practice. Musculoskeletal symptoms in rheumatic conditions are very varied, ranging from mechanical problems to muscular symptoms derived from inflammatory and systemic autoimmune diseases. Several drugs commonly used by different specialists and certain drugs used in rheumatology can also cause a wide variety of muscle symptoms.

A description of different systemic autoimmune diseases follows to describe the different forms of involvement of the musculoskeletal system that they cause, as well as the main causes with which a differential diagnosis should be made.

In this chapter, we will try to give some clues to reach an early diagnosis using clinical criteria, particularly based on a directed anamnesis and physical examination, discussing possible guidelines for the complimentary tests that may be required in patients with muscle complaints.

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Introduction

Muscle complaints are frequently observed in routine rheumatology clinical practice. Sometimes they are a challenge for the specialist, because the symptoms may be nonspecific or difficult for patients to characterize. These muscle complaints can have many different causes. It will be the rheumatologist's job to perform a good diagnostic approach, because these muscle symptoms can be associated with significant disorders, such as systemic rheumatic diseases, particularly systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), systemic sclerosis (SSc), idiopathic inflammatory myopathies (IIM), etc. It is essential to make a differential diagnosis with polymyalgia rheumatica (PMR) and chronic widespread pain, which can also be associated with systemic rheumatic diseases.

The aim of this review is to discuss muscle complaints as common early presenting manifestations of systemic rheumatic diseases and what approach, management and main differential diagnosis should be carried out.

Defining muscle complaints

Myalgia or muscle pain is a complex and subjective feeling in muscles that is difficult to define, qualify, or measure. It is important to differentiate this term from myopathy and myositis. Myalgia is a symptom which may or may not have a pathologically definable cause. Myopathy and myositis are pathological diagnoses.

Myopathy is a pathology based on a deficiency or abnormality in one of the components of the correct functioning of a muscle group (nerve impulse, muscular membrane, proteins responsible for muscle contraction or intracellular metabolism).

Myositis is the inflammation of the muscles and very often it is secondary to an infection or an autoimmune disease.

We must keep in mind other terms when we are talking about muscles. Many patients can use terminology erroneously; hence, the clinician must clarify what the patient is referring to.

Weakness is the loss of strength with difficulty or inability to perform a movement. It may or may not be associated with myalgia.

Muscle fatigue is defined by the inability to continue the movement after several repetitions and recovers with rest. Finally, **asthenia** is the feeling of being tired without objective muscle weakness [1,2].

Practice points

There are different terms when referring to muscle problems.

- Myalgia: muscle pain.
- Myopathy: pathology of some component of the muscle.
- Myositis: muscle inflammation.
- Weakness: loss of muscle power.
- Fatiguability: objective loss of strength with repeated movements.
- Asthenia: subjective feeling of being tired.

Muscle complaints in systemic rheumatic diseases

Systemic sclerosis

SSc is a chronic multisystem disease that is characterized by vascular damage, autoimmune and fibrotic processes. It is associated with high morbidity and mortality rates. SSc is divided into limited cutaneous disease and diffuse cutaneous disease based on the extent of skin thickening. This

unpredictable disease still represents a challenge for rheumatologists and early diagnosis remains a challenge. In fact, SSc is usually diagnosed when the disease is established, and cutaneous fibrosis or involvement of internal systems is already present [3].

The prevalence of muscle involvement in SSc is very diverse between published cohorts, ranging from 9.8% to 35% [4,5].

Pain may not be sufficiently localized to be attributed to an anatomical location, but several pain syndromes have been identified. These include joint contractures, tendon friction rubs, myalgia, myositis, muscle weakness, cutaneous calcifications, synovitis, and compression neuropathies [6].

SSc is one of the most common connective tissue diseases associated with inflammatory myopathies. Jaeger [7] et al. have described that musculoskeletal outcomes are a major determinant of quality of life and function in these patients. In a metanalysis of the Canadian Scleroderma Research Group, pain was present in 85% of the reported patients and proximal weakness in 16.2% which was most frequent in those with early diffuse SSc [8]. Scleroderma myopathy is characterized by mild proximal limb weakness of non-progressive course with normal or slightly elevated creatine phosphokinase (CPK) levels and poor response to corticosteroids. A true myositis was also described but it is less common and characterized by a progressive course with elevation of CPK, typical electromyographic changes and better response to immunosuppressants [9]. Pain and limitation of movement due to skin sclerosis and fibrosis of underlying tissues can also be observed.

In SSc patients, myopathy is not only associated with disability but with lower overall survival rate compared to those patients without muscle involvement [10].

Practice points

- Main pain syndromes in SSc are joint contractures, tendon friction rubs, myalgia, myositis, muscle weakness, cutaneous calcifications, synovitis and compression neuropathies.
- SSc is one of the most common autoimmune diseases associated with myopathy, which is more frequent in early diffuse SSc.
- Myopathy in SSc is associated with higher disability and mortality rate.

Systemic lupus erythematosus

SLE is a chronic systemic autoimmune disease with a wide clinical heterogeneity. The most frequently involved domains are the musculoskeletal and cutaneous.

The musculoskeletal domain symptoms in SLE are one of the most frequent symptoms of these patients, and are part of all classification criteria [11,12].

In some cohorts, musculoskeletal symptoms are present in 90% of SLE patients and are the initial symptoms in around 50% of the cases, articular involvement being the most frequent [13]. Besides, muscle involvement can be present in SLE patients. Even though muscular features are not included in the different SLE classification criteria, they are part of the most used activity indices, such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and British Isles Lupus Assessment Group (BILAG) Index [14,15].

Generalized muscle pain can occur in 49–80% of SLE patients in different published cohorts [16,17]. However, myositis has been described in less than 15% of patients [18–20]. Myositis in SLE correlates with poor prognosis, and therefore, its early diagnosis is extremely important [21–23]. In a German cohort of 339 early SLE patients, fatigue and myalgia (76%) were the most frequent symptoms reported by patients [24].

Myositis in SLE is characterized by proximal muscular weakness, elevated CPK and aldolase levels, and abnormal electromyography. Muscle biopsy may be normal or identical to that of patients with dermato/polymyositis [25].

Liang et al. [26] described that myositis was more common in younger patients and in those with shorter disease duration in a cross-sectional Chinese study of 1,701 SLE patients. Leukopenia, alopecia and active lupus disease were independently associated with myositis and glucocorticoids or immunosuppressive use acted as a protective factor in the development of myositis.

The differential diagnosis with fibromyalgia or with antimalarials or glucocorticoids toxicity is crucial in SLE patients with muscle pain.

Practice points

- Generalized myalgia in SLE is described in 49–80% of cases.
- Muscle pain is one of the most frequently reported symptoms by SLE patients.
- True myositis is rare and is associated with bad prognosis.

Vasculitis

Vasculitis is a heterogeneous group of multisystemic diseases that affect blood vessels and are classified according to the size of the blood vessels mainly affected [27]. Patients often present initially with unspecific symptoms such as fever of undetermined origin, arthralgias and myalgias, before specific vasculitis manifestations appear. Muscle pain in vasculitis was described in 56–76% of patients, frequently in early stages of the disease. "Myalgia, weakness or leg tenderness" are part of the American College of Rheumatology (ACR) Classification Criteria for Polyarteritis Nodosa (PAN), a necrotizing systemic vasculitis that predominantly involves medium arteries [28,29].

There are only a few cases reported in the literature of what Kamimura et al. proposed to call "muscular PAN" [30–36]. This disorder is a localized PAN restricted to the lower limbs and typically presents with intense and intractable bilateral calf pain and swelling and elevated acute phase reactant levels. CPK levels are often normal. Magnetic resonance imaging (MRI) may help to localize the muscles affected and electromyography is usually normal. Biopsy of a symptomatic muscle provided the definite diagnosis of PAN in all reported cases. The response to high-dose oral glucocorticoid therapy is good, although recurrences are not rare.

Practice points

- Myalgias are present in 56–76% of vasculitis patients.
- They are part of PAN classification criteria.
- Muscular PAN is a localized PAN in lower limbs that presents with intense calf pain.
- Histology provides definite diagnosis.

Primary Sjögren's syndrome

pSS is a chronic autoimmune exocrinopathy of unknown etiology. It is mainly characterized by dry mucous membranes, a lymphoplasmacytic infiltrate in the biopsy and the presence of antibodies (ANA, anti-Ro, anti-La and rheumatoid factor). Extraglandular manifestations may be present in 20–30% of the patients [37,38].

The musculoskeletal system is frequently affected in pSS patients, myalgia and weakness being the most common symptoms [39]. In a study of 573 pSS patients, myositis was found in 4.9% [40]. pSS may occasionally be associated with inclusion body myositis. Another cause of myalgia in pSS patients may be axonal polyneuropathy, appearing in approximately 10% [37,41]. Myalgia and fatigue frequently coexist in pSS patients. The prevalence of fibromyalgia (FM) was about 14.6% in the 437 patients analyzed in the Spanish Society of Rheumatology pSS Registry (SJÖGRENSER) [42].

Muscular symptoms are not included in the current ACR/EULAR classification criteria for pSS [43]. However, they are important in the assessment of pSS activity by the ESSDAI index (EULAR SS Disease Activity Index) [44].

Practice points

- Musculoskeletal system involvement is common in pSS usually presenting as myalgia or weakness.
- The prevalence of myositis in pSS patients is about 4.9%.

- Prevalence of fibromyalgia in pSS is about 14.6%.
- Muscular symptoms are relevant in the ESSDAI index, when evaluating pSS activity.

Idiopathic inflammatory myopathies

IIM are a group of chronic, autoimmune conditions primarily affecting the proximal muscles. These disorders are characterized by the presence of an inflammatory infiltrate in the muscle tissue. Patients with IIM usually present subacute muscle weakness with or without myalgia.

Muscular weakness is usually predominantly proximal and symmetrical, typically affecting upper limbs, lower limbs and cervical flexor musculature. However, as the process becomes chronic, there may be involvement of the distal musculature and atrophy due to loss of muscle mass [45].

Inclusion body myopathy is more frequent in males. It occurs only after the age of 40, being the most frequent IIM after the age of 50. It selectively affects deep finger flexors and quadriceps. This myopathy presents in a more insidious way with progression over several years and weakness may even have facial and axial distribution.

Contrary to this, weakness generally develops more rapidly and is more severe in patients with necrotizing autoimmune myopathy [46].

Although IIM are usually painless, myalgias and tenderness are not rare complaints.

Laboratory investigations, including increased CPK and myositis associated antibodies, may help to confirm the diagnosis [47]. Electromyogram is very useful. However, muscle biopsy remains the gold standard for diagnosis [48].

Patients with amyopathic dermatomyositis have typical skin lesions without muscle symptoms, although muscle weakness usually appears during the course of the disease.

Practice points

- The main symptom of IIM is weakness, subacute onset, and proximal and symmetric distribution.
- IIM are usually painless although some types can cause muscle pain, which is related to the activity of the disease.
- In some forms of IIM, there may be distal involvement and atrophy.

Behçet's disease

Behçet's disease is a form of systemic vasculitis with the classical triad of oral ulcers, genital ulcers and uveitis. Musculoskeletal involvement is rare and myositis is the most common manifestation [49]. In single case reports, orbital myositis was reported [50]. Only rarely, myositis may dominate the clinical presentation [51]. Occasionally, myositis may be of the necrotizing type [52].

Practice points

- The most common muscle manifestation in Behçet's disease is myositis, that is not common and is not usually the central clinical feature.

Sarcoidosis

Sarcoidosis is a multisystemic disease of unknown cause characterized by the presence of non-caseating granulomas in various organs [53,54]. Muscle symptoms are not frequent although subclinical myopathy is common in patients with sarcoidosis [55–58]. Three clinical patterns of muscular sarcoidosis have been described: a nodular form occurring in young adults, an acute myositis presentation, and a pseudomyopathic form seen in older patients [59,60]. Muscle pain is present in a high percentage of the patients with clinically active muscular sarcoidosis.

The diagnosis of sarcoidosis is really difficult if myopathy is the first and sole manifestation of the disease.

Practice points

- Although subclinical muscle involvement is very frequent, less than 3% of patients with sarcoidosis have muscular symptoms.

Approach to the patient with muscle complaints

Clinical history

Muscle complaints are one of the main reasons for consultation in rheumatology. It is important for the clinician to make a "pattern recognition" of the various symptoms, signs and clinical information transmitted by the patient. This is useful to identify the main "muscular syndromes" and to distinguish between inflammatory and non-inflammatory diseases, such as fibromyalgia, because this is a leading cause of muscle complaints. This will guide us in the subsequent steps to the diagnosis (physical exam and request of complementary tests).

The family and personal history of systemic rheumatic disorders is of great interest and may provide initial clues for the patient's diagnosis. Comorbidities are also relevant as well as the medication history.

The next and most important step is to ask the patient about his/her pain to define its characteristics and its anatomical origin (muscle, joint, tendon, etc.). Usually joint pain due to arthritis is more localized and can limit both passive and active articular movement. In contrast, muscle pain is more diffuse and difficult to define by the patient; usually only the movement caused by the affected muscle is restricted. Tendon pain is located and usually increases with its passive elongation and contraction against resistance. Other accompanying symptoms such as weakness or cramps may be present and their identification can help define which "muscular pattern" is prevalent, which is a key part of establishing the best diagnostic approach [61].

Some simple questions about different aspects of the pain can help to better define the type of muscle disorder.

A. Chronology: acute or subacute onset.
B. Potential trigger factors: recent infection, new medication, vaccination, exercise, trauma, etc.
C. Influence of activity and rest: inflammatory or mechanical pain.
D. Distribution of the symptoms: localized or diffuse, unilateral or bilateral.
E. Concomitant muscle symptoms: muscle pain, weakness or both.
F. Association of other extramuscular symptoms and signs: asthenia, anorexia, fever, weight loss, sensitive alterations, depression, anxiety, ptosis, diplopia, sleep disorders, skin lesions, etc.

Physical examination

While medical history can provide clues about the cause of the muscle complaint, the physical examination will give us objective signs to confirm whether it is a real muscle disease, as well as defining the location of the disorder and clarifying the diagnosis.

Inspection

The physician must observe the way the patient walks, gets up from a chair, etc. An active search for atrophy, hypertrophy, abnormal movements, swelling or erythema in the area, skin lesions, etc. must be carried out.

Palpation

Exploration of muscle tone may give interesting clues. Muscle tone is regulated by nerve impulses originating in the brain that reach the muscles of the whole body through the motor nerves. Muscle tone is usually normal in myopathies since serious alterations of muscle tone with atrophy only occur

in advanced stages of the disease or in nervous system disorders. Hypertonia occurs when there is some injury in the regions of the nervous system that control the emission of these impulses. Among the diseases that can cause hypertonia are Parkinson's disease, multiple sclerosis, cerebral paralysis, brain tumors and any process that affects the pyramidal pathway.

Muscle strength

Measuring the muscle strength of each muscular group is a difficult task. Muscle strength should always be compared to that in the contralateral site. Physicians should pay special attention to the accurate examination of proximal and flexor neck muscles, as they are the most commonly affected in systemic rheumatic diseases. The most widely used method to explore muscle strength is the Medical Research Council Manual Muscle testing scale [62]. This method involves testing key muscles from the upper and lower extremities against the examiner's resistance and grading the patient's strength on a 0 to 5 scale, from the absence of contraction to normal power (Table 1).

Location

Weakness distribution allows to establish a pattern and localize the site of the lesion. A good interpretation of tendon reflexes, Babinski sign, and sensory defects and a precise identification of the location of the signs are extremely important to differentiate myopathy from diverse neurological syndromes.

Several examples in which location of signs in the physical exam is crucial to the syndromic diagnosis are as follows: a) focal neuropathy (unilateral weakness), b) polyneuropathy (diffuse involvement with weakness and altered sensation), c) mononeuritis multiplex (successive peripheral nerve areas) and d) inflammatory/toxic diseases (proximal musculature and frequent neck flexor musculature involvement).

Other clinical features

Apart from those of muscle involvement, different extramuscular signs can be present in these patients such as several skin lesions (Gottron's papules, heliotrope rash, “shawl sign”, periungual nailfold telangiectasias or “mechanic hands”). Other non-muscular signs that may be present in patients with myopathies are: skin thickening of the fingers, calcinosis, purpura, alopecia, oral or nasopharyngeal ulceration, or signs of arthritis, serositis, pulmonary fibrosis, etc. [63].

Complementary investigations

Clinical history and physical examination lead to an initial clinical suspicion. Then, different complementary tests will guide to a more precise diagnosis. Fig. 1 shows an algorithm of diagnostic use and interpretation of the results of complementary exams in the investigation of patients presenting with muscle complaints.

Table 1
Medical Research Council Manual Muscle testing scale.

Muscle contracts against full resistance	5
Strength reduced, but muscle contracts against some resistance	4
Strength further reduced, muscle contracts only against gravity with examiner's resistance completely removed.	3
Muscle can only move if resistance of gravity is removed.	2
Visible or palpable contraction	1
No movement	0

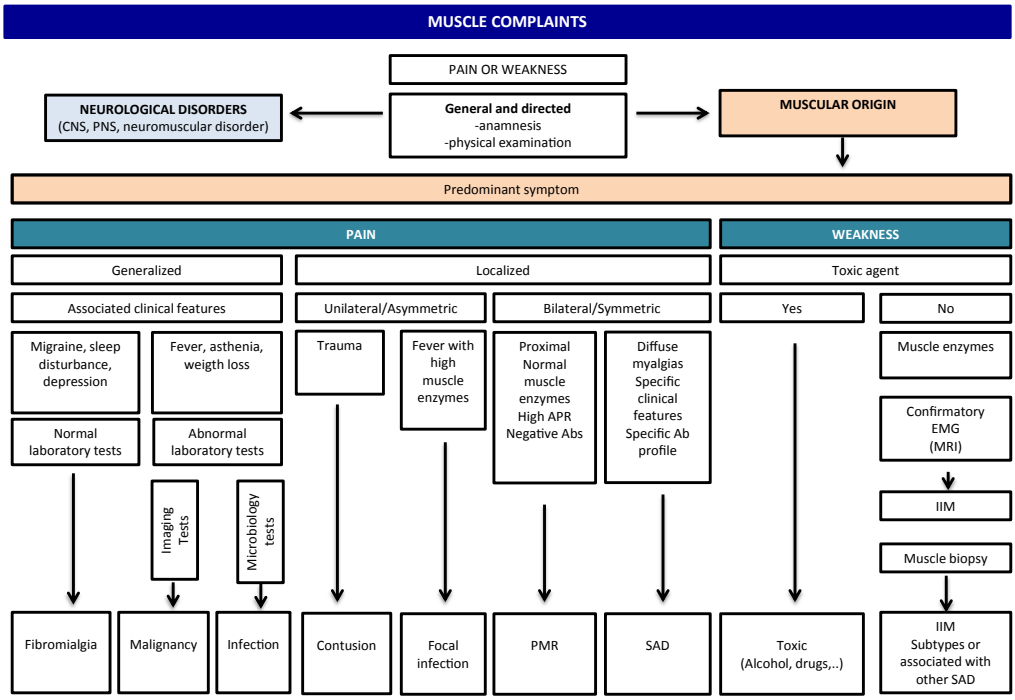

Fig. 1. The patient with muscle complaints. Different clinical scenarios and how to investigate them. APR: acute phase reactants; Abs: autoantibodies; PMR: polymyalgia rheumatica; SAD: systemic autmmune disease; EMG: electromyogram; MRI: magnetic resonance imaging; IIM: idoiiopathic inflammatory myopathy.

Laboratory tests

Plasma muscle enzymes. The first step is to perform a general analysis including complete blood count, urinalysis, renal and liver function measures, thyroid-stimulating hormone (TSH), CPK, aldolase and inflammation markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Muscle enzymes that must be requested to evaluate muscle damage are: CPK, aspartate aminotransferase (AST), alanine aminotransferase (ALT), aldolase and lactate dehydrogenase (LDH). CPK is the most sensitive enzyme for muscle injury [64].

CPK may be elevated for non-pathological reasons: sex, ethnicity, physical exercise, intramuscular injections, or muscle trauma.

A common mistake is the diagnosis of liver disease because of elevated AST and ALT levels from muscular origin. On the other hand, normal muscle enzymes do not exclude the diagnosis of inflammatory myopathy as up to 20% patients with myositis may have a normal range of CPK levels.

The intensity of hyperCPKemia depends on the severity of the myopathy, time of onset and residual muscle mass. Thus, an acute and rapidly progressive presentation of the myopathy causes higher CPK levels and those with more chronic course and loss of muscle mass may have normal CPK values.

Although aldolase values can be increased when there is muscle injury, general consensus has been reached that this biomarker has lower diagnostic performance than CPK in most types of muscle injuries [65,66], so that its measurement may be eventually confined to a very rare subset of patients with myositis and normal CK values [67,68].

LDH is a cytoplasmic enzyme present in the cells of multiple tissues. It rises when there is tissue damage. It is very non-specific, and it represents hemolysis during blood extraction, any process that leads to cell lysis or a neoplastic origin. In context of muscular pathology, it can be elevated in different situations: trauma, intramuscular injection, drugs with muscle toxicity, congenital muscular disease or inflammatory muscle disease. In these cases, the elevation of LDH concentrations is usually

accompanied by the elevation of CPK, AST, ALT and/or aldolase. LDH elevation has a limited clinical value, due to the high rate of false positives [69].

Inflammatory markers. ESR and CRP are non-specific inflammatory markers. They can be elevated by multiple causes. They are useful for diagnosis of different systemic inflammatory rheumatic diseases (e.g.: IIM or polymyalgia rheumatica). Fibromyalgia does not cause high ESR and CRP levels.

Autoantibodies. Autoantibodies have become a support tool in clinical practice when looking for systemic rheumatic diseases. It is not recommended to perform an exhaustive determination of autoantibodies to all patients who present with muscle complaint, since it can cause high false positive results, that can lead to diagnostic and treatment errors. However, they are extremely useful in patients with suspected IIM to guide the diagnosis, establish different clinical phenotypes and get information about prognosis and response to therapies [70].

Autoantibody positivity can occur in the healthy population without having pathological significance. Between 6 and 30% of the general population can present positive ANA so its determination is only recommended in cases with high clinical suspicion of systemic rheumatic disease [71–75]. Table 2 shows the main autoantibodies associated with the different IIM.

Practice points

- Patients with inflammatory myopathies usually have elevated levels of markers of muscle damage (CPK, AST, ALT, aldolase and LDH) and inflammatory markers (ESR and CRP).
- Patients should be carefully selected according to clinical context when performing autoantibody tests. False positive tests can lead to errors in diagnosis and treatment.

Screening for malignancy

Dermatomyositis and polymyositis are associated with malignancy in 25% and 10% of the cases, respectively. The association between necrotizing autoimmune myopathy and cancer has also been described. Most of the tumors are diagnosed within the first year from the myopathy onset although

Table 2
Associated autoantibodies in idiopathic inflammatory myopathies.

Idiopathic Inflammatory Myopathy	Autoantibodies and clinical features
Anti-synthetase syndrome	Anti-PL7: poor prognosis, severe ILD, mild weakness, arthritis Anti-PL12: more likely associated with ILD than myositis Anti-Jo1: more likely associated with myositis than ILD. Arthritis. Better prognosis Anti-OJ: severe weakness and severe ILD Anti-KS: severe ILD Others: anti-ZO, anti-EJ, anti-Tyrosil
Necrotizing myopathy	Anti-SRP: severe weakness, treatment resistance Anti-HMGCR: present in statin-associated myopathies. Associated with cancer
Dermatomyositis	Anti-TIF1-γ: strongly associated with cancer (adults). Dysphagia Anti-NXP2: associated with cancer (adults). Calcinosis and severe weakness Anti-MDA5: amyopathic/pauci-myopathic. Associated with severe ILD and skin ulcerations. Poor prognosis Anti-SAE: severe dysphagia. ILD and cancer in Asian population Anti-Mi2: severe weakness and high serum CPK
Inclusion body myositis	Anti-CN1a
Non-specific myositis	Anti-PM-Scl: associated with systemic sclerosis and SLE. ILD Anti- Ku: associated with systemic sclerosis, SLE and SS. Severe ILD. Anti-SSA (Ro52, Ro60) and anti-SSB(La): associated with systemic sclerosis, SLE and SS, antisynthetase syndrome, rheumatoid arthritis.

ILD: interstitial lung disease; HMGCR: hydroxy-methyl-glutaryl-coenzyme A reductase; SLE: systemic lupus erythematosus; SS: Sjögren's syndrome; CPK: creatine phosphokinase.
Modified from Reference 70.

the diagnosis can take up to 5 years [76,77]. Breast and ovarian cancers are the most common cancers in women and lung and prostate cancers predominate in men with IIM [78].

Data on cancer screening in IIM patients are limited. The European Federation of Neurological Societies recommends that patients with dermatomyositis undergo computed tomography of the chest/abdomen, pelvic ultrasound and mammography in women, ultrasound of testes in men, and colonoscopy in men and women over 50 years of age. If primary screening is negative, a new screening is recommended after 3–6 months and then it is recommended every 6 months for 4 years [79]. In patients with myositis, the CA-125 and CA 19-9 markers may be of interest. Amoura et al. [80] reported that the elevation of serum levels of these two markers as well as the elevation of the CA-125 marker in serial determinations is associated with an increased risk of cancer development, not only of ovarian cancer but also of other types of cancer. They conclude that CA-125 and CA 19-9 could be useful markers of the risk of developing tumors for patients with dermatomyositis and polymyositis and should therefore be included in the search for cancer in these patients, particularly those without interstitial lung disease.

In polymyositis and dermatomyositis patients, the increased risk for malignancy is more significant within the first year of myositis diagnosis and in male patients. The diagnostic testing that should lead to the diagnosis of the neoplasm has been previously discussed [81].

Electrophysiologic studies

Nerve conduction studies and electromyography (EMG) may be helpful to support the diagnosis of inflammatory myopathy or neuropathic process. They can locate the site of the lesion in the peripheral nervous system or muscle and can guide the selection of the most appropriate site for biopsy.

EMG is a sensitive but nonspecific method of evaluating muscle disease and virtually all patients with active myositis have abnormal EMG.

Changes in EMG (short and small motor units, fibrillation, positive pointy waves, insertional irritability and repetitive high-frequency firing) usually occur 2–3 weeks after the onset of the IIM so in acute myopathies it is recommended to perform the study 4 weeks after the onset of symptoms.

EMG should be performed unilaterally and in clinically weak muscles to avoid alterations in the results of the biopsy resulting from the needle itself. Due to disease symmetry, a contralateral muscle that is abnormal by EMG should be chosen for biopsy.

EMG usually does not help to distinguish the etiology of the myopathy. It is useful in myasthenic syndromes, as myasthenia gravis, some congenital myasthenia or the Eaton-Lambert syndrome, in which the EMG, through repetitive stimulation techniques, offers the diagnosis with high specificity. In colchicine myopathy, a mixed pattern with associated neuropathy usually appears.

EMG can also be helpful to distinguish active inflammatory myopathy from glucocorticoid myopathy as in the latter there is a loss of strength due to atrophy and no spontaneous activity is observed [82–84].

Magnetic resonance imaging and ultrasonography

Magnetic resonance imaging (MRI) is the most sensitive imaging tool for detecting muscle abnormalities [85,86]. It is mainly recommended when suspecting IIM and it should always include T1 and a fluid-sensitive sequence, such as T2-weighted fat-suppressed sequences or short-tau inversion recovery (STIR).

The indications for MRI in IIM are [87–89]:

- Documentation of myositis or disease flare. It is an effective assessment for defining the extension and distribution of the disease.
- Directing the site of muscle biopsy as it is more specific than EMG.
- Assessing treatment response as it is able to distinguish chronic active disease from chronic inactive myositis.
- Confirmation of “amyopathic dermatomyositis”.

On the other hand, MRI is an expensive method and it may not always differentiate between inflammatory myopathies and others, such as toxic, metabolic or neuromuscular disorders [87,90].

Whole-body imaging (WBMRI) has become more and more important in recent years. It not only maps the global distribution of the muscle inflammation, but also reveals muscles which may not be evident on clinical examination [91].

Ultrasonography is particularly useful to study patients with PMR, that predominantly affects periarticular structures. Some of the main echographic findings are as follows: signs of bicipital tendonitis, subacromial bursitis, subdeltoid bursitis, trochanteric bursitis and cervical and lumbar interspinous bursitis [92–94].

Muscle biopsy

A muscle biopsy should only be planned after a thorough clinical and diagnostic process. Most patients with systemic rheumatic diseases and myalgias or muscle complaints will not require muscle biopsy. It may be necessary to establish the differential diagnosis between inflammatory, metabolic or necrotizing diseases.

The role of muscle biopsy in the diagnosis of patients with the skin changes characteristic of DM can be cast into doubt and it is not recommended in patients suspected of PMR.

If optimal information is to be obtained, the muscle on which to perform the biopsy must be selected carefully. One must bear in mind that a negative muscle biopsy does not exclude myositis, as inflammatory changes may be focal [95].

The muscle selected for biopsy should be symptomatic. When there is a proximal weakness pattern, quadriceps in legs and deltoids in arms are the most frequently analyzed muscles.

Practice points

- If a directed anamnesis, a thorough physical examination and a clinically guided analytical and serological study are not enough to establish the diagnosis, it may be necessary to carry out neurophysiologic studies such as nerve conduction studies or EMG.
- MRI or ultrasonography may be necessary in some clinical situations.
- More invasive procedures, such as muscle biopsy, can be required on certain occasions to get the precise diagnosis.

Differential diagnosis

Muscle complaints may occur not only in rheumatic conditions but in infectious diseases; neurological, endocrine and metabolic disorders, immunological disease, vascular diseases, hematological disorders, and malignancies (Table 3).

The main rheumatological and non-rheumatological entities underlying muscle complaints in patients are discussed below [96].

In daily clinical practice, the physician has often to make the differential diagnosis between PMR, FM and myositis. Table 4 shows the main distinctive characteristics of these three conditions.

Polymyalgia rheumatica

PMR is an inflammatory disorder characterized by pain and stiffness that symmetrically affects the scapular area and pelvic girdle, and the cervical region. It usually occurs in people older than 50 years of age [97]. Up to 40–50% of patients can have constitutional symptoms that are more frequent if giant cell arteritis is associated [98].

The physical examination highlights the limitation of the active movement of both girdles, more than muscular weakness, and there are no visible signs of arthritis.

ESR and CRP are characteristically elevated and CPK and aldolase levels are normal. Typical findings on ultrasound are signs of bursitis and tenosynovitis and occasionally slight synovitis.

Table 3
Rheumatic and non-rheumatic disorders to consider in the diagnostic workup of muscle complaints.

Rheumatic diseases	Non-rheumatic diseases
Systemic Immune-Mediated Disorders	*Infectious diseases*
• Systemic lupus erythematosus	• Viral infections
• Sjögren's syndrome	• Bacterial infections
• Systemic sclerosis	• Protozoal infections
• Sarcoidosis	• Helminth infections
• Vascular diseases	*Metabolic disorders*
• Behçet's disease	• Hemochromatosis
• Vasculitis	• Amyloidosis
• Idiopathic inflammatory myopathies	• Porphyrias
	• Mitochondrial diseases
Inflammatory joint diseases	*Endocrinological disorders*
• Rheumatoid arthritis	• Diabetes
• Psoriatic arthritis	• Thyroid dysfunction
	Neurological disorders
	• Myasthenia gravis
	• Polyneuropathies
Other rheumatic disorders	*Paraneoplastic syndromes*
• Polymyalgia	*Drugs and muscular toxicity*
• Fibromyalgia	• Alcohol
	• Glucocorticoids
	• Antimalarials
	• Colchicine
	• Statins
	• Vincristine
	• Amiodarone
	• Immune checkpoint inhibitors

Table 4
Differential diagnosis between polymyalgia rheumatica, fibromyalgia and myositis.

	Polymyalgia rheumatica	Fibromyalgia	Myositis
Age	>50 years	25–50 years	More frequent between 40 and 60 years
Sex	Indifferent	90% women	Female/male: 2/1
Location	Cervical, scapular and pelvic girdle	Global	Upper limbs, lower limbs and cervical flexor musculature
Frequency	Frequent	Common	Infrequent
Pain intensity	+++	+++	+/−
Weakness	Not present	Not present	Present
Stiffness	Present	Not present	Not present
Accompanying symptoms	Fever, fatigue, asthenia	Central sensitization syndromes	Dysphagia, dysphonia, hypoventilation
Associated diseases	GCA	Anxiety, depression, migraines, irritable bowel syndrome	Systemic autoimmune diseases, neoplasia
Symptoms onset	Acute	Chronic	Subacute
Distribution	Symmetric	Global	Symmetric
CPK	Normal	Normal	Elevated
EMG	Normal	Normal	Pathological
Antibodies	Negative	Negative	Positive
MRI	Synovitis, tenosynovitis, bursitis	Normal	Muscular edema/atrophy in chronic diseases
Glucocorticoid treatment	Great improvement	Not effective	Intermediate response
Muscle biopsy	Normal	Normal	Inflammatory infiltrate

GCA: giant cell arteritis; CPK: creatine phosphokinase; EMG: electromyography; MRI: magnetic resonance imaging.

Fibromyalgia

FM is a syndrome characterized by chronic diffuse musculoskeletal pain of non-joint origin that is usually accompanied by fatigue, sleep disturbances, anxiety, depression, morning stiffness and cognitive alterations [99]. The 1990 ACR criteria for the classification of FM include the presence of chronic widespread pain for at least 3 months and the existence of at least 11 out of 18 tender points upon palpation [100]. The 2010 ACR diagnostic criteria, unlike the 1990 criteria, recommend the use of a widespread pain index and a scale to measure symptom severity [101]. In 2011, a modification of the 2010 criteria was published that allowed diagnosis to be made entirely by self-report.

FM symptoms vary from one patient to another, although the importance that the patient gives is very high. The course of fibromyalgia is chronic with periods of worsening frequently triggered by situations of stress or other diverse circumstances. The absence of specific findings in the physical examination and the normality of laboratory and imaging tests are essential for the diagnosis of FM.

The coexistence of FM in up to 20% of patients with inflammatory rheumatic diseases makes the differential diagnosis more complex [102].

Drugs and muscular toxicity

Muscle tissue is highly sensitive to many substances. Alcohol is one of the oldest substances known to have adverse effects on muscle tissue, but many substances including commonly prescribed medications can also produce adverse effects. Clinical manifestations of toxic myopathies range from muscle pain to more serious muscle damage leading to rhabdomyolysis. History of drug use is important in the evaluation of patients presenting with various muscle disorders, and the understanding of the pathophysiology of drug-induced myopathy is useful in the management of these patients [103].

Alcoholic myopathy

Alcoholic myopathy is common among people with alcohol use disorder and may manifest as an acute or chronic condition.

Acute alcoholic myopathy is characterized by weakness, pain, tenderness, and swelling of affected muscles. It often occurs after an alcohol binge during a single episode. There is a rhabdomyolysis variant accompanied by elevations in CPK levels and loss of myoglobin in urine, which in severe cases may precipitate acute renal failure.

Chronic alcoholic myopathy presents with progressive proximal muscle weakness over weeks to months. In some cases, patients experience pain, local muscle atrophy, muscle twitching, and/or muscle tightness. It is associated with cumulative lifetime consumption of alcohol [104].

Currently, the only known effective treatment for alcoholic myopathy is complete abstinence from alcohol. Acute alcoholic myopathy usually reverses within days or weeks of abstinence, whereas chronic myopathic changes usually resolve within 2–12 months [105].

Some drugs commonly used to treat rheumatic patients may be the origin of the muscular problem of our patients.

Glucocorticoids (GC)

GC myopathy is produced by direct action of the drug on the muscle. It appears more frequently with the use of fluorinated preparations, such as dexamethasone and triamcinolone. Elderly and sedentary individuals have more risk of muscle toxicity. It usually presents with subacute progressive proximal weakness without pain. These patients usually have other signs of Cushing's syndrome. Muscle enzymes and electromyography are typically normal. MRI images do not show areas of hyper signal in T2. Differentiation between inflammatory and toxic origin is frequently difficult for the rheumatologist. GC myopathy is always a diagnosis of exclusion and a definitive sign is the improvement of weakness after the reduction or withdrawal of GC, which may take up to 3–4 weeks [106].

Antimalarials

Muscle toxicity associated with these therapies occurs by accumulation of the drug, so the clinician must be wary in the case of patients with prolonged exposure. It primarily affects the proximal lower limb muscles, but myocardial involvement and sensitive alterations may occur also. Muscle biopsy is useful in these cases as optical microscopy shows vacuoles and electron microscopy reveals myeloid and curvilinear bodies [107].

Colchicine

Muscular toxicity by colchicine may occur in patients with chronic drug exposure and presents with girdle weakness and occasional sensory neuropathy [108].

Statins

They can cause myalgia, weakness or even rhabdomyolysis. Muscle enzymes may be normal or elevated. It usually occurs in the initial stages of treatment, although it can occur at any time of the exposure [109].

In recent years a new entity called statin-associated immune-mediated myopathy has been described. It is rare and is commonly associated with proximal muscle weakness, higher CPK values, HLA-DRB1 positivity and persistence after statin discontinuation. It may be associated to anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibody. Prompt treatment with immunosuppression and/or immunomodulation is usually of enormous benefit to the patient as it restores muscle strength and physical function [110,111].

Musculoskeletal manifestations due to immune checkpoint inhibitors

The use of immune checkpoint inhibitors to treat cancer is associated with a number of adverse events, including musculoskeletal complication. Arthralgias are the most frequent, but myalgia is not uncommon and even polymyositis, dermatomyositis or eosinophilic fasciitis have been described [112–116].

Others

Vincristine, zidovudine, D-penicillamine, procainamide, interferon-α [106].

Muscle manifestations due to infections

In this situation, the onset of muscular symptoms is usually abrupt and the presence of other clinical findings such as fever, headache, respiratory or gastrointestinal symptoms guides the diagnostic approach. Both in viral and bacterial infections, muscle enzymes are elevated because of rhabdomyolysis. Microbiological tests are key for diagnosis.

Metabolic myopathies

Metabolic myopathies comprise a wide range of muscular disorders that are caused by defects in the cellular energy metabolism. Exercise intolerance, cramps and myoglobinuria are common features. Muscle biopsy (with specific studies) and DNA testing are necessary to lead to the correct diagnosis, which is always a challenge [117].

Paraneoplastic syndromes

Paraneoplastic myopathy has been reported in several neoplasms [81,118]. Lung, gastrointestinal and breast carcinomas may be associated with necrotizing myopathy. The peculiarities in the approach to this clinical situation have been previously described.

Summary

To make a good differential diagnosis when patients present with muscular symptoms as their chief complaint, it is essential for rheumatologists to be aware of the multiple causes that can affect the musculoskeletal system (Table 3). In this regard, close collaboration with other specialists such as neurologists or endocrinologists is of paramount importance.

As soon as the muscle is affected, the strategies shown in the proposed algorithm (Fig. 1) must be implemented in a systematic way, because errors in diagnosis in many of these pathologies can lead to an important deterioration in the health and quality of life of the patient. On the other hand, in most cases, early initial treatment has great prognostic implications in the development of the disease.

A directed anamnesis and a thorough physical examination searching for the coexistence of extramuscular clinical features as well as a compatible basic analytical and serological study can very often lead to a clear diagnosis. In other cases, it may be necessary to extend the study and use neurophysiologic studies such as nerve conduction studies or EMG. More sensitive image tests such as MRI or ultrasonography may be necessary in some clinical situations. More invasive procedures, such as muscle biopsy, can be required on certain occasions to obtain the precise diagnosis.

Sometimes, despite an extensive diagnostic procedure, it is difficult to identify a specific cause of the muscle complaints. In these cases, close collaboration between the multidisciplinary clinical team and an expert muscle pathologist is critical to establish the diagnosis that may lead to a correct therapeutic management of the patient with muscle complaints.

Research agenda

- Development of well-defined guidelines about how to investigate and assess muscle involvement in patients with systemic rheumatic diseases: the promising development of target-oriented drugs in the treatment of these muscular conditions has generated a need to improve the evaluation of the muscular component of the disease to better detect response to therapies.

Conflicts of interest

Authors have no conflicts of interest related with this work.

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