An Updated Approach to the Diagnosis of Inflammatory Myopathies

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ABSTRACT Idiopathic inflammatory myopathies (IIM) are a group of rare, autoimmune, systemic diseases with a large spectrum of clinical phenotypes. The diagnosis and management of myositis demand an integrated evaluation of different clinical, laboratory, and pathological findings in various organs. Recent developments in IIM research, especially in the serological testing and pathology fields, has led to a new classification and better recognition of patients with early or extra-muscular disease, with improvement in clinical care and prognosis.

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KEY WORDS: antisynthetase syndrome (ASyn), dermatomyositis, idiopathic inflammatory myopathies (IIM), myositis-specific antibodies (MSA), polymyositis

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of rare systemic autoimmune disorders, affecting the skeletal muscles, skin, joints, lungs, heart, and gastrointestinal tract. Historically, IIM have been subdivided into dermatomyositis, polymyositis, cancer-associated myositis, and overlap syndrome. Over the past few decades, the discovery of myositis-specific antibodies (MSA) and their correlation to relatively specific clinical and pathological syndromes have led to a revolutionary change in the classification of IIM into four major subgroups: dermatomyositis, immune-mediated necrotizing myopathy (IMNM), inclusion-body myositis (IBM), and antisynthetase syndrome (ASyn), with polymyositis remaining merely a diagnosis of exclusion [1].

THE DIAGNOSIS OF INFLAMMATORY MYOPATHIES REQUIRES AN INTEGRATING APPROACH, BASED PRIMARILY ON THE CLINICAL, LABORATORY, AND IMAGING FINDINGS

IIM are potentially treatable and an early diagnosis with prompt initiation of treatment are of great importance for the patient's prognosis. The diagnosis of IIM, however, can be challenging due to the high variability of clinical presentations and non-rheumatic medical conditions that can mimic myositis. Therefore, a comprehensive approach combining clinical features, serology, and pathological findings is warranted for proper diagnosis. In this review, we portrayed the recent evolution in the approach to a patient with suspected IIM and provided a diagnostic guide.

CLINICAL FEATURES OF IIM

Three distinct clinical presentations of IIM include primarily muscular, extra-muscular dominant, or combined.

Muscle involvement

Symmetrical proximal muscle weakness is the most typical and common IIM muscular symptom. It is usually progressive over weeks or months, but can manifest acutely, especially in IMNM, or insidiously over several years, typically in IBM. Usually, at early stages patients complain of difficulty walking up the hill or climbing stairs, followed by the inability to stand up from an armless chair or comb their hair as the disease progresses. Distal muscles, such as finger flexors and ankle dorsiflexors, can be involved in the early stages of IBM, while in the other subgroups of IIM distal muscle involvement is unusual. Pharyngeal and neck flexors may be affected, causing dysphonia or dysphagia and head drop. The respiratory muscles may be compromised in severe cases. Muscle atrophy develops in a severe and chronic form of the disease.

Muscle weakness is usually painless, although myalgia and muscle tenderness may occur during eruptive phases, especially at disease onset in IMNM, dermatomyositis, or ASyn. The cause of myalgia is attributable to inflammation involving the muscle fascia and nociceptive stimulation from muscle fibers or inflammatory cells. However, when muscle pain is prominent, an alternative diagnosis should be excluded, such as polymyalgia rheumatica, neuropathies or metabolic myopathies, fibromyalgia, infective myositis, or vasculitis.

Muscle strength of different proximal, distal, and axial muscles can be quantitated objectively using manual muscle testing (MMT). This validated score is a useful clinical tool in the diagnosis and monitoring of muscle weakness and has been widely used as a major endpoint in IIM therapeutic trials [2].

Extra-muscular manifestations

Skin

Skin involvement is typical for the dermatomyositis subtype of IIM, can be seen occasionally in ASyn or overlap syndromes, and is absent in patients with polymyositis or IMNM.

Classical cutaneous involvement of dermatomyositis is symmetrical with rashes appearing over sun-exposed areas. The most common and pathognomonic rashes of dermatomyositis are a heliotrope rash, seen as a lilac discoloration of the upper eyelids with periorbital edema, and Gottron's papules or signs, described as erythematous plaques that develop over joint extensors, typically metacarpophalangeal joints and proximal and distal interphalangeal. V-sign is a typical violaceous erythema that can develop over the upper chest and neck, whereas a shawl sign rash occurs over the upper back and shoulders, and holster sign erythema occurs over the lateral surface of the thighs. Additional less familiar skin manifestations of IIM include periungual erythema, mechanic's hands, alopecia, facial erythema, and poikiloderma, which is skin atrophy with hypopigmentation and hyperpigmentation changes and telangiectasia [3]. Of importance, cutaneous manifestations are strongly associated with the presence of specific autoantibodies [Table 1].

Table 1. Clinical and pathological associations of myositis-specific antibodies

Inflammatory myopathy subtype	Pathology findings	Myositis specific antibody	Clinical features	Typical skin manifestation
Dermatomyositis	Perifascicular atrophy, myofiber degeneration and regeneration. perimysial and perivascular inflammatory infiltrate consisting of CD4 > CD8, B cells, macrophages, and dendritic cells, MAC deposition in endomysial capillaries, MHC-1 upregulation	Anti-Mi 2	Prominent muscle involvement, high CK, favorable response to treatment, lower risk of malignancy	Classic dermatomyositis rashes (heliotrope, Gottron's papules, V sign, shawl sign, cuticular overgrowth, photosensitivity)
		Anti-MDA5	CADM, rapidly progressive ILD, arthritis, alopecia	Mucocutaneous ulceration, palmar papules, panniculitis
		Anti-TIF1	High risk of malignancy	Hyperkeratotic palmar papules, psoriasiform lesions, telangiectatic and hypopigmented patches, facial erythema
		Anti-NXP2	Young-onset dermatomyositis, severe muscle disease, edema, high risk of malignancy	Calcinosis cutis
		Anti-SAE	CADM, dysphagia	Dark-red skin rash, rash ulceration, erythroderma
IMNM	Acute myofiber necrosis-scattered degenerating myofibers and myophagocytosis, with fibers in various stages of regeneration, sparse lymphocytic inflammatory infiltrates	Anti-HMGCR	1/3 statin naïve-younger onset and refractory to treatment	No rashes in typical cases
		Anti-SRP	Severe muscle weakness and atrophy, high CK, cardiac involvement, and ILD refractory to treatment	No rashes in typical cases
ASyn	Perimysial infiltrate of mainly lymphocytes and macrophages, perifascicular myofiber necrosis with MHC1 deposition	Anti-Jo-1	Muscle involvement > ILD, arthritis, mechanic's hands, Raynaud phenomenon, less CAM	Typically-mechanic's hand. Can manifest with classical rashes of dermatomyositis, less frequently cutaneous vasculitis, calcinosis cutis, telangiectasia
		Anti-EJ		
		Anti-OJ	Early significant muscle involvement	
		Anti-PL-7	ILD > muscles involvement	
		Anti-PL-12	ILD > muscles involvement	
IBM	Chronic myopathic changes-fiber-size variability, hypertrophy, atrophy, endomysial fibrosis. myofiber invasion by cytotoxic T cells in non-necrotic fibers, CD8 > CD4, amyloid-like material, rimmed vacuoles	Anti-C1NA	Indolent distal weakness, frequently asymmetrical bulbar, and respiratory involvement, poor prognosis in IBM	No rashes in typical cases

ASyn = antisynthetase syndrome, CADM = clinically amyopathic dermatomyositis, CAM = cancer-associated myositis, CK = creatine kinase, EJ = glycyl, IBM = inclusion-body myositis, ILD = interstitial lung disease, IMNM = immune-mediated necrotizing myopathy, Jo-1 = anti-histidyl, MAC = membrane attack complex, OJ = isoleucyl, PL-7 threonyl, PL-12 = alanyl

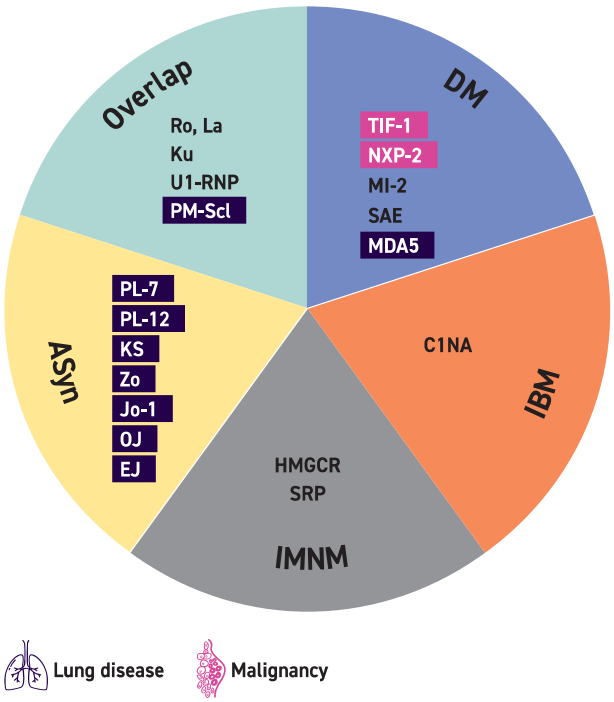
Lung

The lung is one of the most common extra-muscular targets in IIM. A recent meta-analysis found pulmonary involvement in 40% of IIM patients [4]. The growing prevalence of lung disease in IIM may be attributed to an increase in awareness and the routine use of high-resolution computed tomography (HRCT).

ASyn and clinical amyopathic dermatomyositis (CADM), especially anti-MDA-5 positive dermatomyositis, are more prone to develop interstitial lung disease (ILD). ILD can occur prior to, parallel with, or following muscular symptoms of IIM. For example, more than half of IIM patients positive for PL-7 or PL-12 antibodies present with sole lung involvement at the stage of the first evaluation [5]. No direct correlation exists between the extent and severity of ILD with the degree of muscle disease activity. However, the presence of ILD in IIM is associated with worse outcomes compared to IIM without ILD. The most frequent histological pattern of IIM–ILD is nonspecific interstitial pneumonia (NSIP). Other patterns, including usual interstitial pneumonia (UIP), organizing pneumonia (OP), and diffuse alveolar damage (DAD) can be seen as well, but are less common. HRCT is considered the imaging modality of choice for ILD detection.

Figure 1. Current classification of idiopathic inflammatory myopathies by myositis-specific antibodies

ASyn = antisynthetase syndrome, CADM = clinically amyopathic dermatomyositis, CAM = cancer-associated myositis, CK = creatine kinase, EJ = glycyl, IBM = inclusion-body myositis, ILD = interstitial lung disease, IMNM = immune-mediated necrotizing myopathy, Jo-1 = anti-histidyl, KS = asparaginyl, OJ = isoleucyl, PL-7 threonyl, PL-12 = alanyl, PM = polymyositis, Zo = phenylalanyl



Heart

Cardiac involvement is frequent in IIM, with a reported incidence of 10–70%. Autopsy reports demonstrate inflammatory infiltration and fibrosis of the myocardium resembling the findings in the skeletal muscles in IIM patients. Cardiac involvement is often subclinical, manifesting in nonspecific electrocardiogram changes and echocardiographic abnormalities. Late gadolinium enhancement consistent with myocardial fibrosis can be detected in 47% of IIM patients on cardiac magnetic resonance tomography [6]. In symptomatic patients, heart failure is the most frequent manifestation. Since cardiac involvement is a major prognostic factor for death in IIM patients, early detection and treatment are crucial, with a recommendation for routine periodic electrocardiograms and echocardiography tests for all patients with IIM patients [7].

Gastrointestinal tract

Dysphagia is a common manifestation in IIM patients, with a prevalence reported in up to 84% of cases, most frequently in patients with IBM [8]. Dysphagia is usually oropharyngeal, with difficulties in the initiation of deglutition and risk for aspiration pneumonia and mortality. In addition, esophageal and intestinal dysmotility can manifest with a wide spectrum of gastrointestinal symptoms including postprandial abdominal pain, bloating, watery diarrhea, and malabsorption. Rare gastrointestinal complications include mucosal ulceration and hemorrhage or ischemia secondary to vasculitis, especially in children with juvenile dermatomyositis, pneumatosis cystoides intestinalis, and total gut failure with atonic bowel.

Other extra-muscular manifestations

Arthritis is a well-recognized symptom of IIM, with a prevalence of up to 50%, particularly frequent in the ASyn subgroup at disease onset. The most typical presentation is polyarthritis, involving the hands, with possible deformities resembling rheumatoid arthritis (RA). An erosive disease is uncommon and occurs mainly in patients presenting with IIM–RA overlap with a positive rheumatoid factor (RF) or anti-citrullinated peptide antibodies (ACPA), and in patients with anti-Jo-1 positive ASyn. Constitutional symptoms including low-grade fever, malaise, and weight loss are commonly seen in cases of ASyn and overlap myositis but can also be seen in other IIM subgroups. Fever is common in ASyn and is present in 25% of patients during the disease course.

DIAGNOSTIC APPROACH TO A PATIENT WITH SUSPECTED IIM

The current diagnostic approach for IIM is based on the integrated evaluation of muscle enzyme levels, primarily creatine phosphokinase (CK) values, serological testing, electromyography, magnetic resonance imaging (MRI), and muscle biopsy [9].

Muscle enzymes level

The serum CK levels are elevated in most IIM patients and are considered the most sensitive marker of muscle inflammation and damage. The evaluation of CK values can serve as a diagnostic tool, for monitoring the response to treatment, and as an indicator of disease relapse. Changes in CK level often precede the clinical manifestation; elevation of CK may appear before clinical exacerbation of muscle weakness is apparent, and conversely, the CK levels may decrease in response to therapy weeks or even months prior to the improvement of muscle strength. The CK levels vary widely, but usually increase by more than 10-fold above the upper limit of normal (ULN) in untreated cases and can increase to more than 50-fold above ULN in cases of IMNM. Less frequently, CK values may be within normal limits, mostly in IIM associated with malignancy or IBM, but several reports demonstrated normal CK levels in up to 25% of dermatomyositis patients [10].

MYOSITIS-SPECIFIC ANTIBODIES ARE ASSOCIATED WITH DISTINCT CLINICAL PHENOTYPES AND PATHOLOGICAL FEATURES, AND CARRY PROGNOSTIC SIGNIFICANCE

Other muscle-derived enzymes including lactate dehydrogenase (LDH), aldolase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are usually elevated as well in IIM and can be used for the diagnosis. Interestingly, some studies demonstrated elevated aldolase levels in up to 75% of IIM patients with normal serum CK levels.

Serology

The identification of MSA and their clinical significance began in the 1970s with the discovery of Mi-2 antibodies, followed by anti-Jo1, anti-threonyl-tRNA synthetase antibodies (PL-7), and more. It remains an evolving process to this day with novel antibodies identified every few years. Besides their role as useful biomarkers for diagnosis, MSA are associated with a typical clinical subset and pathological findings and carry prognostic importance [Table 1] [Figure 1]. The first suggestion that MSA status is a more useful guide than the clinical group in assessing patients with myositis was made as early as 1991 by Love and colleagues [11]. The 2017 European League Against Rheumatism/ American College of Rheumatology (EULAR/ACR) classification criteria for IIM incorporated only anti-Jo1 antibodies status [12]. However, the most recent classification criteria published over the last few years by the European Neuromuscular Centre (ENMC) of dermatomyositis [13] and IMNM [14], comprised MSA in their classification, demonstrating that clinical and laboratory features together with relevant MSA are sufficient for the classification purposes. Nevertheless, there are some limitations to MSA testing. First, only about 60% of IIM patients are seropositive for MSA. Furthermore, new commercial line blot assays carry a lower positive predictive value (PPV) compared to traditional immunoprecipitation with more cases of false-positive results. Hence, MSA testing is recommended only in patients with clinical suspicion of IIM, and interpretation should be done with caution, with MSA serving as supporting evidence in suitable cases. Multiple MSAs rarely coexist in a single patient (0.2% of cases); therefore, when multiple MSAs are detected, a high level of suspicion is warranted [15].

However, myositis-associated antibodies (MAA), including anti-SSA, anti-Ku, anti- polymyositis/SCL, anti-U1-RNP, and anti-U3-RNP, primarily described in overlap myositis with other connective tissue diseases, may coexist with positive MSA. Although less specific, clinical phenotype and prognosis have been associated with MAA as well. For example, anti-Ro-52kD antibodies, which are highly prevalent in patients with ASyn with positive anti-Jo1 antibodies or dermatomyositis patients with positive anti-MDA5 antibodies, were shown to be associated with more severe and rapidly progressive ILD with poorer prognosis [16,17], as well as more severe muscular involvement, joint impairment, and increased risk of cancer [18].

Electromyography

Needle electromyography is an electrodiagnostic test used to record the electrical activity in the muscle. It can help distinguish myopathy from neurologic disease and other IIM mimics such as toxic exposures or inherited disorders and can serve as a method to differentiate active disease from an inactive one, with weakness secondary to steroid usage or disuse myopathy. An additional value of electromyography includes identifying the highest yield biopsy sites and assessing response to therapy. An electromyography study can be performed on several muscle groups, depending on the pattern of weakness, with increased yield when performed on clinically weak muscles. Characteristic electromyography findings of muscle irritability include short, small, low amplitude polyphasic motor unit potentials; fibrillation potentials at rest; and increased insertional activity. Positive sharp waves and complex repetitive discharges support myopathic disease. Electromyography has a reported 82% sensitivity, 76% specificity, 95% positive predictive value, and 40% negative predictive value for the diagnosis of IIM [19].

However, electromyography poses some limitations. First, myopathy findings are not specific to IIM, and it is important to exclude other myopathies. In addition, steroid usage prior to electromyography testing can result in a higher false-negative rate. Last, the test is operator-dependent and requires skill and expertise.

Magnetic resonance imaging

Muscle magnetic resonance imaging (MRI) is a useful imaging technique for IIM diagnosis, assessment of disease activity, and response to treatment during follow-up. MRI can visualize diverse muscle pathology, including muscle edema, fatty replacement, and atrophy. It can provide information regarding the distribution of muscle involvement, reveal muscle involvement that was undetected during a clinical examination, and help guide muscle biopsy [20].

Axial T1-weighted sequences are useful for identifying anatomy and evaluating fatty atrophy, whereas muscle edema is best detected with fluid-sensitive sequences such as short tau inversion recovery (STIR) or fat-suppressed T2-weighted sequences. The administration of gadolinium in T1 fatty-saturated sequences can help visualize muscle inflammation with similar potential but is not superior to that of STIR or fat-suppressed T2-weighted sequences. In dermatomyositis, involvement of the subcutaneous connective tissue septa and the muscle fasciae may also be seen [21]. Distinctive MRI patterns in IBM include fatty infiltration and atrophy with more common involvement of the distal quadriceps, sartorius, and medial gastrocnemius compared to the pelvis muscles, in relatively asymmetric distribution [22].

The reported sensitivity rate of skeletal muscle MRI is up to 90% for the diagnosis of IMM, but it is often nonspecific. A common pitfall in interpreting muscle MRI is equating muscle edema with IIM, while muscle edema on MRI can be seen in various conditions, including infectious myositis, trauma, rhabdomyolysis, subacute denervation, and radiation therapy. It can even exhibit a physiologic finding during and briefly after exercising [23].

Muscle biopsy

Developments in serological testing and imaging for the diagnosis of IIM led the paradigm away from histopathology-based diagnosis to an integrated approach considering clinical, serological, and imaging findings [24]. Thus, muscle biopsy is no longer considered an essential tool for IIM classification according to IMNM and dermatomyositis as well as the latest EULAR/ACR classification criteria for IIM [12]. However, it is important to perform muscle biopsy in unclear cases, particularly in seronegative IIM patients, to allow the correct classification and avoid confusion with IIM mimics. The yield of a muscle biopsy is higher when guided by physical examination, electromyography, and imaging studies [25].

MUSCLE BIOPSY IS NO LONGER CONSIDERED AN ESSENTIAL TOOL FOR IDIOPATHIC INFLAMMATORY MYOPATHIES (IIM) CLASSIFICATION BUT IS OF IMPORTANCE IN UNCLEAR CASES, PARTICULARLY IN SERONEGATIVE IIM PATIENTS, TO ALLOW THE CORRECT CLASSIFICATION AND AVOID CONFUSION WITH IIM MIMICS

The main histopathological findings consistent with dermatomyositis are perifascicular atrophy and microangiopathy. The inflammatory infiltrates in dermatomyositis are mainly comprised of B cells and CD4+ T helper cells, which are located primarily at perivascular sites or within the interfascicular septa [26]. The histopathological hallmark of IMNM is scattered necrotic and regenerating muscle fibers at various stages of regeneration with infiltration of degenerate muscle fibers by macrophages and sparse mononuclear cell infiltrates [26], while the main pathological features in ASyn are perifascicular necrosis and fragmentation with perimysial alkaline phosphatase positivity [27]. Classic muscle biopsy findings in IBM are chronic myopathic changes, endomysial inflammation with myofiber invasion by cytotoxic T cells, and presence of amyloid-like material [26]. The formation of rimmed vacuoles, small areas of focal destruction of muscle fibers, is known as characteristic of IBM but can be found in a variety of disorders, including metabolic myopathies, muscular dystrophy, motor neuron disease, endocrine disorders, or drug-induced myopathy. Their presence can be demonstrated by simple hematoxylin and eosin (H&E) staining but are better visualized using more specific stains such as trichrome staining, modified gomori trichrome (mGT), and congo red staining [28-30]. Fixation in formalin precludes the performance of histochemical and various immunohistochemical techniques and often leads to inconclusive or unspecific results. Therefore, the examination of liquid nitrogen frozen specimens is imperative for a complete neuromuscular investigation [25].

CANCER-ASSOCIATED MYOSITIS

IIM, particularly dermatomyositis, are associated with an increased risk of malignancy. Malignancy involves mainly solid organs, including lung, stomach, bladder, ovaries, breast, and cervix. The risk is higher in the first year following IIM diagnosis but may persist beyond the fifth year after IIM onset [31]. The association was well-established in numerous large-population epidemiologic studies, with an estimated risk of malignancies in IIM being 2–7 times higher than in the general population. Clinical risk factors for cancer-associated myositis (CAM) include older age at disease onset, male sex, dysphagia, cutaneous necrosis, ulceration, vasculitis, rapid onset of myositis, and refractory myositis. However, ILD, arthropathy, and Raynaud phenomenon are associated with a lower risk of cancer [32]. Autoantibodies associated with the greatest increase in the risk of cancer in myositis include anti-TIF1-gamma, carrying a 9.3-fold higher risk of cancer, and antinuclear matrix protein-2, with a 3.6-fold higher risk of cancer. In addition, malignancy was reported in 14–57% of patients with anti-SAE antibodies [33].

Current recommendations for cancer screening in IIMs rely on the risk level and point to the importance of assessing a comprehensive history and a physical examination of the patient. The use of routine total body computed tomography or 18F-fluorodeoxyglucose positron-emission tomography, and tumor markers remains controversial. These techniques are usually recommended for the examination of patients with a high risk for CAM [34].

CONCLUSIONS

IIM diagnosis requires an integrated clinico-sero-pathological approach and can be challenging in cases of atypical, amyopathic, or predominant extra-muscular manifestations. The classification has been constantly evolving over the years, with dermatomyositis, IMNM, ASyn, and IBM constituting clinically, histologically, and pathogenically distinct categories of IIM. MSAs are specific and helpful in diagnosis and classification. Muscle biopsies are relevant in uncertain cases.

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The world is changed not by the self-regarding, but by men and women prepared to make fools of themselves.

Phyllis Dorothy James, Baroness James of Holland Park, OBE, FRSA, FRSL, known professionally as P.D. James (1920–2014), English novelist and life peer

Of all the preposterous assumptions of humanity over humanity, nothing exceeds most of the criticisms made on the habits of the poor by the well-housed, well-warmed, and well-fed.

Herman Melville (1819–1891), American novelist, short story writer, essayist, and poet