REVIEW ARTICLE

Inflammatory Myopathies

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SUMMARY

Inflammatory myopathies are a heterogeneous group of autoimmune diseases characterized by immune-mediated damage to skeletal muscle. They are classified into five major subtypes: inclusion-body myositis, immune-mediated necrotizing myopathies, antisynthetase syndrome, overlapping myositis, and dermatomyositis, each with distinct clinical features and outcomes. Inclusion-body myositis and immune-mediated necrotizing myopathies primarily affect muscle, with prognosis largely determined by functional impairment, whereas antisynthetase syndrome, overlapping myositis, and dermatomyositis are systemic diseases that can involve the skin, joints, and lungs and may be life-threatening. The majority of inflammatory myopathies are associated with myositis-specific autoantibodies, which inform diagnosis, subtype classification, and prognosis. Advances in understanding the distinct pathomechanisms underlying each subgroup now enable increasingly targeted therapeutic approaches.

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N Engl J Med 2026;394:1925-38.
DOI: 10.1056/NEJMra2415426

CME

IDIOPATHIC INFLAMMATORY MYOPATHIES ARE A COMPLEX GROUP OF AUTOimmune disorders that are characterized by inflammatory muscle-tissue infiltrates. Historically conceptualized as idiopathic, these conditions are now recognized as immune-mediated myopathies with nuanced pathophysiological mechanisms. The terminology regarding polymyositis[1] and dermatomyositis[2] emerged in 1886 and 1891, respectively. Bohan and Peter established definitive diagnostic criteria in 1975,[3] which differentiated entities on the basis of dermatologic manifestations. Subsequent refinements in the classification of inflammatory myopathies have delineated critical subcategories: antisynthetase syndrome in 1990,[4] inclusion-body myositis in 1995,[5] and immune-mediated necrotizing myopathies in 2004.[6] Each subcategory has distinct phenotypic characteristics with myopathological features and specific autoantibodies.[7] Many of the conditions previously referred to as polymyositis may also occur in the spectrum of other systemic autoimmune conditions, such as systemic sclerosis or mixed connective-tissue diseases, now referred to as overlapping myositis. However, a small number of patients have been identified whose diseases do not align with any of these subcategories. These cases are currently being referred to as polymyositis, but this entity is now considered relatively rare.[8] Although the entity of dermatomyositis has not been questioned, subgroups with distinct prognoses have been identified on the basis of specific autoantibodies. This review critically examines the contemporary understanding of these complex autoimmune myopathies, with discussion of the progressive refinement of their classification, pathogenic mechanisms, and current and future treatments.

EPIDEMIOLOGY

Idiopathic inflammatory myopathies are rare diseases, with an incidence estimated by means of a meta-analysis of 0.79 per 100,000 person-years and a prevalence of 14 cases per 100,000 persons.[9] However, substantial variations are observed depending on region and case definitions.[10-12] As with other rheumatic autoimmune diseases, idiopathic inflammatory myopathies affect female persons more frequently, with the notable exception of inclusion-body myositis, which occurs more often among male persons.[9] Dermatomyositis can occur at any age, but when it appears before the age of 15 years, it is generally referred to as juvenile dermatomyositis. Immune-mediated necrotizing myopathies, antisynthetase syndrome, and overlapping myositis are rare in children. Inclusion-body myositis almost always begins after 35 years of age and most often appears in affected persons at approximately 60 years of age.[13] Although idiopathic inflammatory myopathies are acquired diseases, they have a notable genetic component that affects susceptibility. Genomewide association studies have identified the HLA region as the most strongly associated area, with distinct patterns across subgroups.[14] Heritability is estimated to be as high as 24% in identical twins,[14] a statistic that emphasizes the influence of environmental factors, both infectious[15] and noninfectious[16] (e.g., smoking, ultraviolet radiation, cancer, and certain medications such as statins). Immune checkpoint inhibitor–induced myopathy is a specific immune-related adverse event in the field of oncology that falls outside the scope of this review.

CLINICAL FEATURES

MUSCLE INVOLVEMENT

The hallmark of idiopathic inflammatory myopathies is muscle involvement (Fig. 1). Mode of onset, topography of weakness, muscle-enzyme levels, and myopathological features characterize the different subgroups. Inclusion-body myositis manifests as a slowly progressive condition with asymmetrical muscle weakness, particularly affecting the quadriceps and finger flexors — a distribution that is almost pathognomonic.[17] Creatine kinase levels in patients with inclusion-body myositis may range from normal to moderately elevated.[18] Magnetic resonance imaging (MRI) often reveals both inflammation and fatty replacement of myofibers in the deep finger flexors and quadriceps.[18]

Immune-mediated necrotizing myopathies show rapid progression in the majority of cases, primarily affecting the lumbopelvic region,[19] with characteristically high creatine kinase levels. MRI of the muscles in patients with immune-mediated necrotizing myopathy may reveal signs of disease activity (T2-weighted hyperintense signal) in the pelvifemoral muscle groups and lumbar regions and muscle damage with fatty replacement of myofibers (T1-weighted hyperintense signal), which is commonly observed in patients in whom treatment is delayed.[20]

In antisynthetase syndrome, muscle deficits are symmetric, proximal, and subacute on presentation and are typically moderate in severity despite frequent substantial elevations in creatine kinase levels.[7] Of note, in approximately one third of patients with antisynthetase syndrome, myositis may not develop, but characteristic organ involvement (see below) may develop during the course of the disease, with marked variation depending on the specific antisynthetase syndrome autoantibodies present.[21]

At least one third of patients with dermatomyositis may have mild or no muscle weakness, a condition known as amyopathic dermatomyositis.[7] When muscle weakness is present, it typically manifests as symmetrical weakness, with the deltoid muscles commonly affected first. Creatine kinase levels in dermatomyositis may be normal and notably do not correlate with muscle weakness.

EXTRAMUSCULAR FEATURES

Although dermatomyositis and antisynthetase syndrome may present with skeletal muscle signs, extramuscular involvement can dominate the clinical picture at disease onset (Fig. 2). In contrast, inclusion-body myositis and immune-mediated necrotizing myopathy do not show appreciable extramuscular manifestations.

Skin lesions are a hallmark of dermatomyositis, although skin changes are also common features of antisynthetase syndrome and overlapping myositis. The classic dermatomyositis skin rash consists of a heliotrope rash that affects the upper eyelids and periorbital region; erythema on the hands involving metacarpopha-

langeal joints, proximal interphalangeal joints, and periungual areas; and Gottron's papules, which appear as violaceous, scaly papules. Gottron's sign, erythematous macules and patches that overlay the elbows and knees, is a less specific but nonetheless suggestive sign. Additional cutaneous manifestations include malar erythema, often extending to create a V sign on the upper chest and a shawl sign on the upper back. Nonphotoexposed areas of skin may also be affected, including the scalp (sometimes with alopecia), lower back, and the sides of the thighs (holster sign). It should be noted that a small percentage of patients (8%) have no skin signs (known as dermatomyositis sine dermatitis) and are often positive for anti-NXP2 (nuclear matrix protein 2) autoantibodies.[22] Raynaud's phenomenon is commonly observed in dermatomyositis and antisynthetase syndrome, but severe vasculopathy with skin ulcerations occurs predominantly in patients with dermatomyositis who are positive for anti-MDA5 (melanoma differentiation–associated protein 5) autoantibodies. Mechanic's hands, marked by hyperkeratotic and fissured lesions on the fingertips, are indicative of antisynthetase syndrome but can also manifest in patients with anti-MDA5–positive dermatomyositis. Finally, some patients with antisynthetase syndrome may present with dermatomyositis-type rashes; however, distinct clinical manifestations differentiate these patients from those with classic dermatomyositis (e.g., mechanic's hands, Raynaud's phenomenon, arthritis, interstitial lung disease, or cardiac involvement).[23]

Bilateral and symmetric polyarthritis is frequently observed in patients with antisynthetase syndrome, overlapping myositis, and anti-MDA5–positive dermatomyositis. A notable shared feature among these conditions is the prevalence of interstitial lung disease, which affects more than 80% of patients and can be the predominant or even sole manifestation at the onset of the disease.

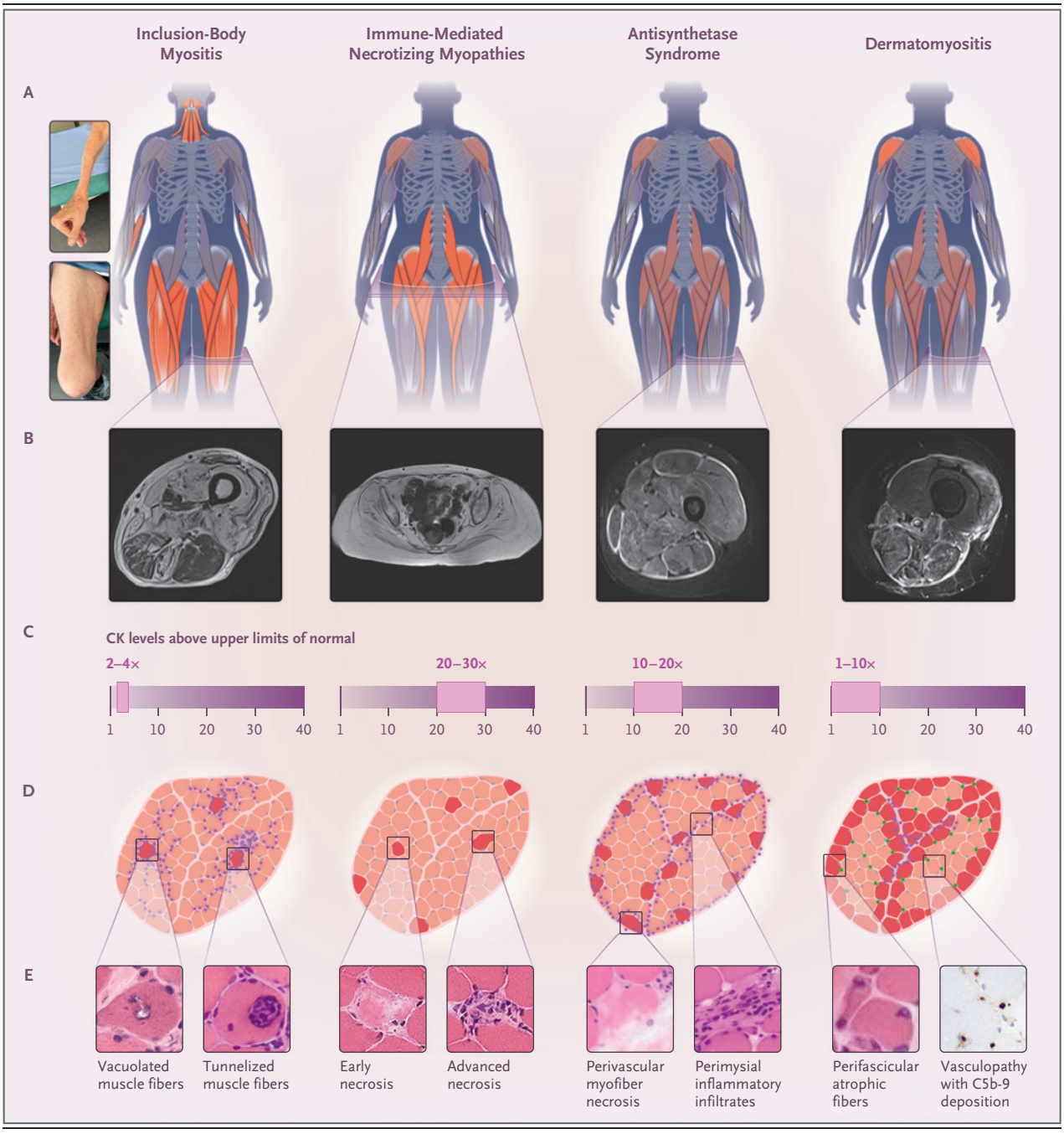
DIAGNOSIS AND CLASSIFICATION

AUTOANTIBODY FEATURES

Approximately 70% of patients with myositis have detectable autoantibodies,[24] and the identification of myositis-specific autoantibodies and myositis-associated autoantibodies has revolutionized the diagnosis and classification of idiopathic inflammatory myopathies. The first myositis-specific autoantibody was isolated from a patient with dermatomyositis, Mrs. Mi, in 1976,[25] and today approximately 30 myositis-specific autoantibodies have been identified. These antibodies are generally mutually exclusive and have characteristic phenotypes (Table 1).[7] Dermatomyositis-specific autoantibodies include anti–Mi-2, anti–TIF-1γ (transcriptional intermediary factor 1γ), anti-SAE (small ubiquitin-like modifier–activating enzyme), anti-NXP2, and anti-MDA5. In antisynthetase syndrome, although eight specific antibodies can be routinely identified with immunoassays, three predominant types (anti–Jo-1 [histidyl-tRNA synthetase], anti–PL-7 [threonyl-tRNA synthetase], and anti–PL-12 [alanyl-tRNA synthetase]) account for more than 90% of cases.[23] Immune-mediated necrotizing myopathy is associated with two specific antibodies: anti-SRP (signal recognition particle) and anti-HMGCR (3-hydroxy-3-methylglutaryl–coenzyme A reductase). The anti-cN1A (cytosolic 5′-nucleotidase 1A) antibody, although prevalent in inclusion-body myositis, lacks specificity because it can also be found in patients with Sjögren's syndrome, those with systemic lupus, and patients with no muscle involvement.[30]

Myositis-associated autoantibodies occur in the context of other connective-tissue disorders in which muscle involvement is part of the disease spectrum, but also in patients who have only myositis. The primary myositis-associated autoantibodies include anti-Ro52/Ro60, anti–U1-RNP (U1 ribonucleoprotein particle), anti-Ku, and anti–PM/Scl.[31] With the exception of anti-Ro antibodies, myositis-associated autoantibodies are usually not associated with myositis-specific autoantibodies.[32]

Conventional screening methods that use human epithelial type 2 cells often lack the sensitivity required for routine detection of myositis-specific autoantibodies and myositis-associated autoantibodies, necessitating the use of multiplex commercial immunoassays.[28] The reliability of these tests is generally good, although reliability can vary depending on the specific myositis-specific autoantibody being tested. Some antibodies, such as anti–TIF-1γ, anti-SAE, anti-EJ (glycyl-tRNA synthetase), anti-OJ (isoleucyl-transfer RNA synthetase), anti-Zo (phenylalanyl-tRNA synthetase), and anti-cN1A, have been observed to produce less-reliable results (Table 1).[28] Therefore,



consideration of the clinical data and muscle biopsy results and correlation of these with immunoassay results are essential in order to limit errors in interpretation.[28] Clinicians should consider these antibodies only in the right clinical context and should consider repeating testing with the use of reference standard methods in cases of suspected false-positive or false-negative results.

In the context of an idiopathic inflammatory myopathy, the reliable detection of a myositis-specific autoantibody with appropriate tests enables the diagnosis and subtyping of the disease. For instance, in a patient with a typical derma-

Figure 1 (facing page). Patterns of Muscle Involvement in the Four Major Types of Idiopathic Inflammatory Myopathies.

Shown is a comparative analysis of four idiopathic inflammatory myopathy subtypes. Panel A shows the distribution of muscle weakness (dark red areas indicate severe and frequent involvement) and typical muscle atrophy of finger flexors and quadriceps in inclusion-body myositis. Panel B shows characteristic MRI images (corresponding to either muscle damage or muscle edema). Panel C shows elevations in creatine kinase (CK) levels above the upper limit of normal (pink shading). Panel D is a schematic diagram of the pathological features showing affected muscle fibers (red areas), inflammatory infiltrates (purple dots), and vascular changes when present (green dots); and Panel E shows key microscopic findings (400× magnification). In the depiction of a patient with inclusion-body myositis, key specific features are involvement of the muscles of swallowing, finger flexors, and quadriceps; MRI (axial T1-weighted image of left thigh) showing fatty infiltration of the quadriceps with undulating fascia sign; pathological features, including scattered fiber damage and dense endomysial inflammation within the muscle fascicles; and key findings such as vacuolated or tunnelized muscle fibers, often surrounded by lymphocytes. In the example of a patient with immune-mediated necrotizing myopathy, the proximal muscles (scapular and pelvic girdle, with the pelvis predominant) are primarily affected. MRI (axial T1-weighted image of pelvic girdle) shows complete fatty infiltration of the gluteus muscles in a patient with very severe muscle damage. Pathological testing shows minimal inflammation with random fiber damage and muscle fibers in various stages of necrosis, from early (hyalinized fibers) to advanced (macrophage-mediated clearance). As shown in the illustration of antisynthetase syndrome, the proximal muscles (scapular and pelvic girdle) are primarily affected. MRI (axial T2-weighted short tau inversion recovery relaxation image of left thigh) shows muscle hypersignal corresponding to inflammation as well as the disease activity and fascia hypersignal that are frequently observed in patients with antisynthetase syndrome. Pathological evaluation shows characteristic perifascicular myofiber necrosis with perimysial inflammatory infiltrates and perivascular inflammation. Like immune-mediated necrotizing myopathy and antisynthetase syndrome, dermatomyositis primarily involves proximal muscles (scapular and pelvic girdle, with the scapula predominant). MRI (axial T2-weighted short tau inversion recovery relaxation image of left thigh) shows edema related to the degree of inflammation and disease activity in muscle and subcutaneous tissue. Pathological testing further shows clustered fiber damage at the fascicle periphery but with atrophic fibers, as well as perivascular inflammation with vasculopathy illustrated by endocapillary C5b-9 deposition.

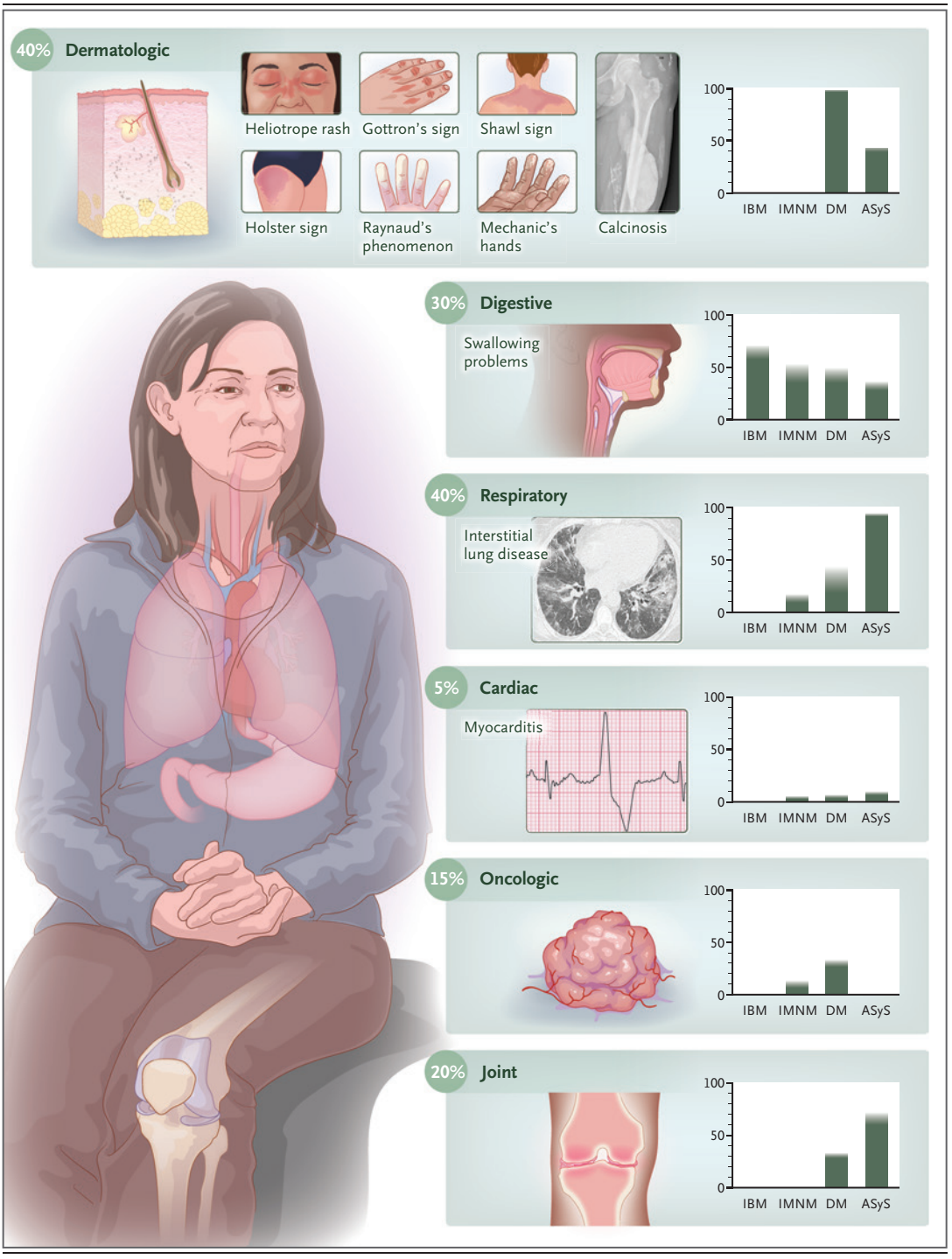
tomyositis skin rash, a high creatine kinase level, and anti-Mi2 autoantibodies, dermatomyositis is diagnosed.[33] Similarly, a patient with proximal muscle weakness and anti-SRP autoantibodies is classified as having immune-mediated necrotizing myopathy,[34] and a patient with anti–Jo-1 autoantibodies, interstitial lung disease, and polyarthritis receives a diagnosis of antisynthetase syndrome.[35] The first American College of Rheumatology and European Alliance of Associations for Rheumatology (ACR/EULAR) diagnostic criteria for idiopathic inflammatory myopathies,[36] which introduced the use of myositis-specific autoantibodies to diagnose idiopathic inflammatory myopathies, were based on one antibody (anti–Jo-1). This limitation prevented subclassification of polymyositis (e.g., antisynthetase syndrome or immune-mediated necrotizing myopathy). The ACR/EULAR criteria, which include other myositis-specific autoantibodies, are currently under review.

MUSCLE AND SKIN PATHOLOGIC FEATURES

Each clinicobiologic idiopathic inflammatory myopathy subgroup has a characteristic myopathological pattern (Fig. 1).[37] Muscle biopsy remains the reference standard for diagnosing idiopathic inflammatory myopathies and their subgroups, although it requires substantial expertise. Although muscle biopsy is no longer mandatory for diagnosing idiopathic inflammatory myopathy in patients with well-defined clinical–serologic presentations, it remains an essential test for patients without myositis-specific autoantibodies and for all diagnoses of inclusion-body myositis.[18] In patients with myositis-specific autoantibody-negative dermatomyositis, particularly those with amyopathic presentations, skin biopsy offers an alternative diagnostic approach by revealing characteristic dermatopathologic features, specifically vasculopathy and interface dermatitis.[33]

DIFFERENTIAL DIAGNOSIS

The diagnostic process presents several important challenges, particularly in patients who have muscle-dominant disease with a slowly progressive disease onset. A primary concern is distinguishing early-onset immune-mediated necrotizing myopathies from genetic myopathies in persons younger than 30 years of age. In this



context, the presence of seropositivity in immune-mediated necrotizing myopathies becomes particularly valuable for diagnosis, underscoring the importance of myositis-specific autoantibody detection.[38] However, the diagnostic process becomes more complex in seronegative cases, in which careful evaluation of muscle pathological features and response to treatment is crucial for an accurate diagnosis. Myopathological analysis not only fosters diagnostic accuracy but also pro-

Figure 2 (facing page). Spectrum of Extramuscular Involvement in the Four Main Groups of Idiopathic Inflammatory Myopathy.

Shown are the most common types of tissue involvement in idiopathic inflammatory myopathy. For each subgroup of myositis, the frequency of tissue involvement is shown on a bar chart. Respiratory involvement (nonspecific interstitial pneumonia or organized pneumonia) and skin lesions (erythematous) are the most common manifestations. The most common dermatological manifestations (erythematous or not) are heliotrope rash (dermatomyositis [DM]), Gottron's papules (DM), shawl sign (DM), holster sign (DM), Raynaud's phenomenon (DM, antisynthetase syndrome [ASyS], and overlap myositis), mechanic's hands (ASyS), and calcinosis (skin damage). Digestive involvement is dominated by dysphagia. The presence of cancer of any type is common. Symptomatic cardiac involvement is rare and may be associated with ventricular dysfunction, arrhythmias, or conduction disorders. IBM denotes inclusion-body myositis, and IMNM immune-mediated necrotizing myopathy.

vides information about severity of the involvement and facilitates ruling out other diseases from the differential diagnosis. Further complicating the diagnostic process is the fact that in the case of some dystrophies, considerable inflammatory infiltrates are regularly shown on muscle biopsy, as seen in conditions such as dysferlinopathies[39] and facioscapulohumeral muscular dystrophy.[40] A lack of improvement after treatment with glucocorticoid agents should arouse suspicion of either a genetic myopathy or inclusion-body myositis. In patients in whom muscle signs present subacutely, clinicians must also consider drug-induced myopathy and hypothyroidism. Infectious myositis that leads to specific treatment, such as cases due to human immunodeficiency virus, trichinellosis, or leptospirosis, remains a very rare cause of myositis but should be considered. A muscle biopsy may also provide useful information about such rare conditions, including details about the specificity of the underlying process.

PROGNOSIS

Myositis is one of the most severe chronic autoimmune diseases, affecting both functional and vital outcomes through musculoskeletal and extramusculoskeletal involvement, including an association with cancer. These effects vary on the basis of the specific idiopathic inflammatory myopathy entity involved, age of onset, and duration of disease progression, with myositis-specific autoantibodies serving as crucial prognostic indicators (Table 1).

PROGNOSIS FOR SURVIVAL

Mortality associated with idiopathic inflammatory myopathies is approximately 10% in the first year after diagnosis,[26] with cancer and respiratory complications as the leading causes of death. The association with cancer is particularly important, with cancer developing in approximately 10% of adult patients within 3 years before or after diagnosis.[26] Dermatomyositis, older age, male sex, dysphagia, and cutaneous ulceration are associated with a significantly increased risk of cancer,[41] whereas antisynthetase syndrome, overlapping myositis, inclusion-body myositis, and Raynaud's phenomenon are associated with a lower risk.[26] As shown in Table 1, cancer risk stratification is contingent on idiopathic inflammatory myopathy subtypes and autoantibody status.[26] Accordingly, recommendations for cancer screening are made on the basis of risk.[26]

Respiratory involvement (Fig. 2) is another important prognostic factor, affecting more than 80% of patients with antisynthetase syndrome and anti-MDA5–positive dermatomyositis and certain subgroups of patients with overlapping myositis. In antisynthetase syndrome, 10-year survival is 70% among patients who are anti–Jo-1 positive and 47% among patients who are non–anti-Jo-1 positive (anti–PL-12, anti–PL-7, anti-EJ, anti-KS, or anti-OJ).[21] The most common causes of death among patients with idiopathic inflammatory myopathies are pulmonary fibrosis and pulmonary hypertension.[21] On the other hand, anti-MDA5 autoantibodies are associated with a particularly poor prognosis owing to rapidly progressing interstitial lung disease in 30% of cases and mortality exceeding 50%.[42] Bulbopharyngeal muscle involvement with swallowing difficulties is an additional severity criterion because of the associated risk of respiratory complications. Although rare, other life-threatening conditions exist, including severe myocarditis in antisynthetase syndrome, overlapping myositis, or immune-mediated necrotizing myopathy and digestive vasculopathy in anti-NXP2–positive dermatomyositis.[43]

Table 1. Myositis-Specific and Myositis-Associated Autoantibody Features.*

IIM Subtype and Autoantibody	Immunoassay Available?	Assessment of Immunoassay Quality†	Clinical Features or Prognosis	Cancer Risk[26]
Inclusion-body myositis				
Seronegative				Low
Anti-cN1A	Yes	Awareness of limitations indicated	Worse prognosis than seronegative IBM	Low
Immune-mediated necrotizing myopathy				
Seronegative				High
Anti-HMGCR	Yes	Acceptable	Better muscle function prognosis in patients who have received statins than in those who have not	Intermediate
Anti-SRP	Yes	Acceptable	Severe weakness, frequent mild ILD	Low
Antisynthetase syndrome				
Anti–Jo-1	Yes	Acceptable	Most frequent, classic phenotype (myositis, arthritis, ILD)	Low
Anti–PL-7	Yes	Acceptable	Worse prognosis owing to more severe ILD	Low
Anti–PL-12	Yes	Acceptable	Worse prognosis owing to more severe ILD	Low
Anti-EJ	Yes	Awareness of limitations indicated	Constant ILD	Low
Anti-OJ	Yes	Serious concerns	Frequent ILD, arthritis and fever	High[27]
Anti-KS	Yes	Acceptable	Frequent amyopathy, sicca syndrome	Low
Anti-Zo	Yes	Awareness of limitations indicated	Classic phenotype (myositis, arthritis, ILD)	Low
Anti-Ha	Yes	Awareness of limitations indicated	Predominant muscle involvement, frequent skin lesions, infrequent ILD	Low
Other‡	No	Immunoassays not yet available for routine detection		Low
Dermatomyositis				
Seronegative				High if age >40 yr at onset
Anti–TIF-1γ	Yes	Awareness of limitations indicated	Psoriasis-like, poikiloderma, ovoid palatal patch	High
Anti-NXP2	Yes	Acceptable	Intestinal vasculopathy, skin edema, calcinosis	High
Anti–Mi-2	Yes	Acceptable	High creatine kinase level, photodistributed rash	Intermediate
Anti-MDA5	Yes	Acceptable	Severe ILD, amyopathic, arthritis, cutaneous ulcers	Intermediate
Anti-SAE	Yes	Awareness of limitations indicated	OP ILD pattern, “angel wing” rash on back	Intermediate

Table 1. (Continued.)

IIM Subtype and Autoantibody	Immunoassay Available?	Assessment of Immunoassay Quality†	Clinical Features or Prognosis	Cancer Risk[26]
Overlap myositis				
Seronegative				Low
Anti-PM/ScL	Yes	Acceptable	NSIP or OP ILD pattern, skin thickening, sclerodactyly	Low
Anti-Ku	Yes	Acceptable	Arthralgia, ILD, glomerulonephritis, sclerodactyly	Low
Anti-RNP	Yes	Acceptable	ILD, arthralgia, sclerodactyly	Low

* Anti-cN1A denotes anti–cytosolic 5′-nucleotidase 1A, anti-EJ anti–glycyl tRNA synthetase, anti-Ha anti–tyrosyl tRNA synthetase, anti-HMGCR anti–3-hydroxy-3-methylglutaryl-coenzyme A reductase, anti–Jo-1 anti–histidyl tRNA synthetase, anti-KS anti–asparaginyl tRNA synthetase, anti-Ku, anti-MDA5 anti–melanoma-differentiation antigen 5, anti–Mi-2 anti–nucleosome-remodeling deacetylase complex, anti-NXP2 anti–nuclear matrix protein 2, anti-OJ anti–isoleucyl tRNA synthetase, anti–PL-7 anti–threonyl tRNA synthetase, anti–PL-12 anti–alanyl tRNA synthetase, anti-PM/ScL anti-polymyositis/scleroderma, anti-RNP anti-ribonucleoprotein, anti-SAE anti–small ubiquitin-like modifier activating enzyme, anti-SRP anti–signal recognition particle, anti–TiF-1γ anti–transcriptional intermediary factor-1γ, anti-Zo anti–phenylalanyl tRNA synthetase, IBM inclusion-body myositis, IIM idiopathic inflammatory myopathy, ILD interstitial lung disease, IMNM immune-mediated necrotizing myopathy, NSIP nonspecific interstitial pneumonia, and OP organizing pneumonia.

† Assessments of the quality of assays for the respective antibodies reflects the consensus of participants in a European Neuromuscular Center workshop.[28]

‡ Other antisynthetase myositis-specific antibodies that are not yet routinely detectable are: anti–cysteinyl tRNA synthetase, anti–lysyl tRNA synthetase, anti–glutaminyl tRNA synthetase, anti–tryptophanyl tRNA synthetase, anti–seryl tRNA synthetase, anti–arginyl tRNA synthetase, anti–methionyl tRNA synthetase, and anti–valyl tRNA synthetase.[29]

MUSCULOSKELETAL-FUNCTION PROGNOSIS

The prognosis for muscle function directly correlates with the extent of muscle damage, with the most severe outcomes observed in cases that remain untreated. The replacement of normal muscle tissue by atrophic fibroadipose tissue, visible on muscle MRI or with muscle pathological testing, leads to irreversible weakness. This muscle damage manifests most severely in immune-mediated necrotizing myopathy and inclusion-body myositis (Fig. 1).[20] Inclusion-body myositis follows a particularly challenging course, characterized by progressive fatty replacement of muscle that typically necessitates assistance with walking within 10 years after diagnosis.[13] It is encouraging to note that motor impairment frequently shows positive progress after the initiation of treatment in patients with dermatomyositis and antisynthetase syndrome. Joint involvement in antisynthetase syndrome or overlapping myositis generally maintains a nondestructive pattern.

PATHOPHYSIOLOGICAL FEATURES

The relative phenotypic homogeneity observed in the four subgroups of idiopathic inflammatory myopathies reflects distinct underlying pathomechanisms. Accordingly, transcriptomic analysis of muscle tissue reveals four characteristic molecular signatures that further differentiate these conditions.[44]

Inclusion-body myositis stands out as a distinct form of myositis, characterized not only by its unique onset pattern and deficit topography but also by its poor response to glucocorticoid treatment. With regard to pathophysiological features, inclusion-body myositis uniquely combines muscle inflammation with degenerative changes.[45] The inflammatory component features activated CD8+ T lymphocytes showing oligoclonal expansion and terminal differentiation.[45,46] These lymphocytes exert cytotoxic effects against muscle fibers within a cytokine environment dominated by interferon-γ.[45] The degenerative aspects manifest through rimmed vacuoles, accumulation of protein aggregate, and signs of endoplasmic reticulum stress, along with dysfunction in autophagy and mitochondrial processes.[18] The relationship between these autoimmune and degenerative mechanisms remains a topic of active debate. However, recent evidence from xenograft models indicates that degenerative mechanisms can evolve independently.[47]

Immune-mediated necrotizing myopathy dis-

plays a distinctive pathophysiological pattern characterized by necrotic myofibers and predominant endomysial macrophagic infiltrates with a specific type of autophagy (sarcoplasmic fine granular p62 pattern).[48] The presence of immunoglobulin and complement deposits on myofibers, combined with the ability to induce myopathy in mice through patient serum transfer, suggests a pathogenic role for immune-mediated necrotizing myopathy-specific autoantibodies.[49] Although this hypothesis faces challenges owing to the intracytoplasmic location of antibody targets and the limited success of anticomplement therapy,[50] recent discoveries provide new supporting evidence. These include the identification of genetic myopathy secondary to HMGCR loss of function[51] and the discovery that anti-HMGCR antibodies are internalized into the myofibers of patients with immune-mediated necrotizing myopathy.[52] This hypothesis is reinforced by the fact that in vitro, anti-HMGCR antibodies inhibit HMGCR activity.[53] The encouraging outcomes observed with allogeneic CD19-targeted chimeric antigen receptor T-cell (CAR-T) therapy[54] further substantiate the notion of a pathogenic role for B cells.

Antisynthetase syndrome manifests with characteristic perifascicular muscle-fiber necrosis accompanied by T-cell infiltrates[55] as well as B-cell and plasma-cell niches[36] that show immune signatures distinct from dermatomyositis. A growing body of evidence implicates the Jo-1 antigen in disease pathogenesis, particularly in lung tissue. Animal models that use either passive transfer of anti–Jo-1 antibodies or Jo-1 protein immunization suggest a pathogenic role for the humoral response.[56] This hypothesis gains further support from successful outcomes reported with CD19-targeted CAR-T therapy.[57]

Dermatomyositis exhibits a distinctive interferon type I signature in muscle and skin tissues, as well as in blood samples.[58] The pathophysiological picture includes vasculopathy and perifascicular myofiber atrophy. Laboratory studies have shown that interferon type I, particularly interferon-β, has cytotoxicity toward both muscle and endothelial cells.[59] The observation that genetic interferonopathies, characterized by excessive and dysregulated interferon type I production, manifest with similar vasculopathy has led to the conceptualization of dermatomyositis as an acquired interferonopathy.[60] Notably, all dermatomyositis-specific antibodies have been shown to target proteins involved in the interferon pathway, with experimental data suggesting pathogenic involvement.[61]

TREATMENTS

Treatment strategies must balance the need for initial remission induction with long-term maintenance therapy, with attention paid to the distinct pathologic mechanisms underlying each subtype. Inclusion-body myositis presents a unique therapeutic challenge, because no controlled prospective trials have shown clear benefits from conventional treatments. Standard immunosuppressive approaches — including intravenous immune globulin (IVIG), glucocorticoids combined with IVIG, and methotrexate — have failed to show efficacy[45] and may actually worsen muscle weakness.[13,62] Attempts to target degenerative mechanisms or enhance muscle mass have similarly disappointed, with recent large-scale trials of arimoclomol[63] and bimagrumab[64] failing to show clinically significant benefits over placebo.

For other idiopathic inflammatory myopathy subtypes, high-dose glucocorticoids remain the primary option for inducing disease remission. The high risk of relapse during glucocorticoid tapering necessitates concurrent immunosuppressive treatment for maintenance, typically involving antimetabolites such as methotrexate, azathioprine, or mycophenolate mofetil. Although the initial results of a trial of rituximab appeared to be disappointing,[65] the early primary end point and mixed patient population (consisting of patients with polymyositis and those with dermatomyositis) may have obscured potential benefits for specific subgroups.

Therapeutic approaches must now be targeted according to the myositis subgroups. For immune-mediated necrotizing myopathy, guidelines recommend high-dose glucocorticoids combined with methotrexate.[34] Anti-HMGCR–positive patients often receive additional IVIG, whereas anti-SRP–positive patients may benefit from rituximab.[34]

With regard to antisynthetase syndrome, recent data highlight the importance of B-cell depletion therapy. Rituximab therapy has resulted in favorable responses in patients with antisynthetase syndrome as compared with patients with

other myositis-specific autoantibodies, particularly those who are seronegative.[66] Rituximab has also shown efficacy in treating interstitial lung disease associated with idiopathic inflammatory myopathies, particularly in antisynthetase syndrome.[67] In antisynthetase syndrome interstitial lung disease, other open or retrospective studies suggest the benefit of treatment with mycophenolate mofetil, azathioprine, cyclophosphamide, or calcineurin inhibitors.[68]

The treatment of rapidly progressive interstitial lung disease, commonly seen in anti-MDA5–positive dermatomyositis and sometimes in antisynthetase syndrome, consists of intensive combination therapy comprising high-dose glucocorticoids and multiple immunosuppressive agents. The most commonly reported combination includes glucocorticoids, cyclophosphamide, and calcineurin inhibitors. However, other triple therapies that include agents such as Janus kinase (JAK) inhibitors, rituximab, or mycophenolate mofetil have also been reported, and recent guidelines have proposed triple therapy without specifying the combination.[69] Nevertheless, it should be noted that the benefit of rituximab may be delayed in this fulminant condition. Lung transplantation may be an option in refractory cases.[69]

A randomized trial in juvenile dermatomyositis[70] showed that glucocorticoid monotherapy is less effective than glucocorticoids combined with methotrexate or cyclosporine in terms of preventing relapse, but the combination of glucocorticoid–cyclosporine has a worse side-effect profile than the glucocorticoid–methotrexate combination; therefore, the current recommendation for adult dermatomyositis is also to combine glucocorticoids with methotrexate.[70] In a randomized controlled trial, IVIG has shown efficacy in significantly reducing disease activity in patients with dermatomyositis.[71] At present, IVIG stands as the sole therapy for dermatomyositis that has received approval, as substantiated by a phase 3 trial, and is endorsed by regulatory agencies. This trial constitutes the foundation for the majority of contemporary clinical trials in the domain of idiopathic inflammatory myopathy. However, the position of IVIG within the therapeutic armamentarium remains to be fully delineated.

Across all idiopathic inflammatory myopathy subtypes, physical exercise has proven beneficial rather than harmful, contributing to improvements in endurance, strength, and quality of life.[72] A combined program of aerobic and resistance exercises, performed three times weekly, is now strongly recommended as part of comprehensive disease management.

THERAPEUTIC PERSPECTIVES

The revision of classification frameworks and a better understanding of pathophysiological mechanisms are opening up increasingly targeted therapeutic perspectives. Immunomodulation targeting cytotoxic T cells remains a promising approach for controlling inclusion-body myositis disease activity. Notwithstanding the negative primary outcome of rapamycin (sirolimus) in a phase 2 trial,[73] the positive secondary outcomes have led to the initiation of a phase 3 trial (ClinicalTrials.gov number, NCT04789070). A phase 2–3 trial of an anti-KLRG1 monoclonal antibody (NCT05721573) targeting terminally differentiated effector cells within muscle infiltrates has recently been completed.

Trials of treatment for immune-mediated necrotizing myopathy, antisynthetase syndrome, and dermatomyositis are underway to assess reducing the half-life of autoantibodies through FcRn receptor blockade (NCT05523167 and NCT05379634). Other antibody-depletion strategies have shown success with daratumumab[74] and CD19-targeted CAR-T therapy.[75]

Similarly, B-cell depletion therapy (anti-CD19 CAR-T therapy) shows promising results[57] in antisynthetase syndrome, even in patients with severe interstitial lung disease, although long-term data are still pending. In addition, nintedanib, an antifibrotic drug that has shown promise in reducing interstitial lung disease progression in different connective tissue disorders,[76] is currently under clinical trial for myositis-associated interstitial lung disease (NCT05799755).

For dermatomyositis, preliminary studies indicate the potential benefits of therapies that target the interferons through the use of JAK inhibitors.[77,78] Controlled therapeutic trials are underway with these molecules (NCT04972760) and tyrosine kinase 2 (TYK2) inhibitors (NCT05695950), which block the intracellular signaling pathway downstream of the interferon type I receptor. As reported by Vleugels et al. in this issue of the *Journal*, the use of brepocitinib (a dual TYK2–JAK1

KEY POINTS

INFLAMMATORY MYOPATHIES

- Inflammatory myopathies are a heterogeneous group of autoimmune diseases defined by immune-mediated damage to skeletal muscle tissue.
- Inflammatory myopathies are subdivided into inclusion-body myositis, immune-mediated necrotizing myopathies, antisynthetase syndrome, myositis occurring in the spectrum of connective-tissue diseases (overlapping myositis), and dermatomyositis.
- In inclusion-body myositis and immune-mediated necrotizing myopathies, muscle involvement is predominant and the prognosis is primarily functional.
- Antisynthetase syndrome, overlapping myositis, and dermatomyositis are systemic diseases that can affect the skin, joints, and lungs and can be life-threatening.
- The majority of inflammatory myopathies are associated with a myositis-specific autoantibody, the presence of which determines the diagnosis, subtype, and prognosis.
- Each myositis subgroup is characterized by distinct pathomechanisms that now allow for targeted therapeutic approaches.

inhibitor) resulted in significant benefits.[79] Other approaches are also under investigation, including monoclonal antibodies targeting the interferon type I receptor (NCT06455449) or the interferon-β cytokine (NCT05192200). The role of dermatomyositis-specific autoantibodies remains to be elucidated; however, isolated cases report the effectiveness of daratumumab in severe anti-MDA5–positive dermatomyositis[80] and of anti-CD19 CAR-T in a case of seronegative juvenile dermatomyositis.[81]

CONCLUSIONS

The management of idiopathic inflammatory myopathies has evolved, reflecting advancements in clinical immunopathological testing. The refinement of the diagnosis and classification of these myopathies through the identification of myositis-specific autoantibodies has helped clarify the challenges of each patient subgroup, as well as the underlying pathologic mechanisms. These advancements have led to substantial changes in the therapeutic landscape of idiopathic inflammatory myopathies, supported by major breakthroughs in hemato-oncology therapies. Key innovations include interferon pathway blockers for dermatomyositis, antibody-depletion therapy that has shown promising results in severe antisynthetase syndrome and immune-mediated necrotizing myopathy, and new drugs that are being tested for the treatment of inclusion-body myositis. The results of ongoing clinical trials will provide further insights into the effectiveness of these treatments.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Prof. Serge Herson, M.D., former head of our department, who established the department's large cohort of patients on which our clinical experience is based; Sarah Leonard Louis, M.D., for providing the histopathological images shown in Figure 1; and the following collaborators who have been involved in our scientific works about idiopathic inflammatory myopathies — Bérénice Tendrel, M.S., Damien Amelin, M.S., Julian Sanchez Dal Cin, Ph.D., Aude Rigolet, M.D., Nicolas Champtiaux, M.D., and Pascale Daniel, M.D.

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