Immune and Inflammatory Myopathies

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Andrew R. Findlay and Robert C. Bucelli

Key Points

1. Immune and inflammatory myopathies (IIM) are characterized by weakness with immune or inflammatory changes on muscle biopsy and commonly have extra-muscular manifestations.
2. Unique clinical features, autoantibodies, and histopathological patterns are used to phenotypically categorize patients and predict treatment response and prognosis.
3. The most commonly agreed-upon criteria recognize four main categories: dermatomyositis, sporadic inclusion body myositis, antisynthetase syndrome, and immune-mediated necrotizing myopathy.
4. Excluding sporadic inclusion body myositis, IIM treatment still largely relies on empirical use of corticosteroids and steroid-sparing agents.

Introduction

Immune and inflammatory myopathies (IIM), collectively known as myositis, are characterized by progressive weakness and inflammatory cellular infiltrates within skeletal muscle. Damage to specific tissues within skeletal muscle, such as connective tissue or blood vessels, may cause syndromes involving multiple organ systems other than muscle, including skin, lungs, and joints. IIM subtypes have historically been defined by clinical and histopathological differences and traditionally were classified as polymyositis (PM) or dermatomyositis (DM). Progress has been made in revising Bohan and Peter's original diagnostic criteria from 1975 in order to more accurately align clinical, autoantibody, and histopathological data with prognosis and response to treatment [1, 2]. PM has been overvalued [3, 4], and pathologic criteria isolated two new subgroups, previously referred to as PM, including sporadic inclusion body myositis (sIBM) [1, 2] and immune-mediated necrotizing myopathy (IMNM) [2]. These classification approaches, however, define overlapping entities. For example, antisynthetase syndrome is often classified as DM, as PM, or as an overlap syndrome [5–7]. Myopathology [8] and autoantibodies can help define subgroups of patients in terms of clinical or pathologic phenotypes, prognosis, and response to treatment [9–13]. The most up-to-date, and commonly accepted, classification

A. R. Findlay (✉) · R. C. Bucelli
Department of Neurology, Neuromuscular Section, Barnes Jewish Hospital, Washington University School of Medicine in Saint Louis, Saint Louis, MO, USA
e-mail: arfindlay@wustl.edu

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criteria will be used in this chapter and eliminates PM as a distinct entity recognizing only DM, IMNM, sIBM, and antisynthetase syndrome [14]. PM does not represent a subgroup of patients, and use of this term should probably be discontinued [14]. It is important to recognize that all classification criteria have their drawbacks. A major issue with the criteria used for this chapter is that it fails to account for other forms of IIM, such as brachio-cervical inflammatory myopathy, focal myositis, eosinophilic myositis, and granulomatous myopathies. This chapter describes current knowledge of the epidemiology, clinical characteristics, diagnostic evaluation, classification, pathogenesis, treatment, and prognosis of IIM.

Epidemiology

Most epidemiologic studies have used criteria that fail to distinguish sIBM, IMNM, and antisynthetase syndrome (discussed previously), causing inaccuracies in incidence and prevalence studies and making it easier to analyze data for IIM as a collective group. Incidence rates for IIM range between 4.27 and 7.89 per 100,000 person years, and prevalence ranges from 9.54 to 32.74 cases per 100,000 individuals [15–17]. sIBM prevalence has been reported as 9.3 per million [18]. Using recent classifications, of all IIMs, sIBM accounts for 29.6%, IMNM 35%, DM 20%, and antisynthetase syndrome 15.4% [14]. DM, IMNM, and antisynthetase syndromes occur more frequently in females [19]. DM may affect children and adults [19], whereas sIBM is seen more commonly in male patients over the age of 50 [20]. Mean annual medical costs and number of ambulatory visits, specialty visits, and inpatient hospital stays are significantly higher among subjects with IIM compared to matched controls [21].

Clinical Features

Dermatomyositis

Dermatomyositis may present with subacute onset progressive proximal weakness, cutaneous manifestations, or both [22]. The deltoids tend to be more severely affected [14]. Some patients may present with only skin changes and are considered to have hypomyopathic or amyopathic forms of disease [23]. Others may present with isolated muscle weakness and never develop rash or only develop rash months later [24]. Juvenile patients may present initially with a febrile illness [24]. Pathognomonic skin features include violaceous periorbital edema (heliotrope rash) and papular lesions on the extensor surfaces of metacarpophalangeal and interphalangeal joints, Gottron's papules (Fig. 20.1a). Other findings may include an erythematous rash over extensor surfaces of limbs (Gottron's sign), over the neck and chest (V sign), and over the back of the neck and shoulders (shawl sign), limb edema, alopecia, skin ulcers, calcinosis, and panniculitis (Fig. 20.1b–f) [14]. Lesions may be photosensitive and pruritic [25]. Juvenile patients more commonly develop cutaneous calcinosis (30–70% of juvenile cases and 10% of adult cases) over pressure points [25, 26]. Myalgias may also be present [27].

Immune-Mediated Necrotizing Myopathy

IMNM is typically characterized by rapid progression of severe proximal weakness, with prominent involvement of the psoas muscles and exceptionally high creatine kinase (CK). Toxic or drug-induced etiologies, as well as some hereditary myopathies (e.g., limb-girdle muscular dystrophy), may appear similar to IMNM and should be ruled out [28–30]. Patients may have mild myalgias or have no muscle pain whatsoever [31]. Extra-muscular manifestations are generally mild if they occur [32–34].

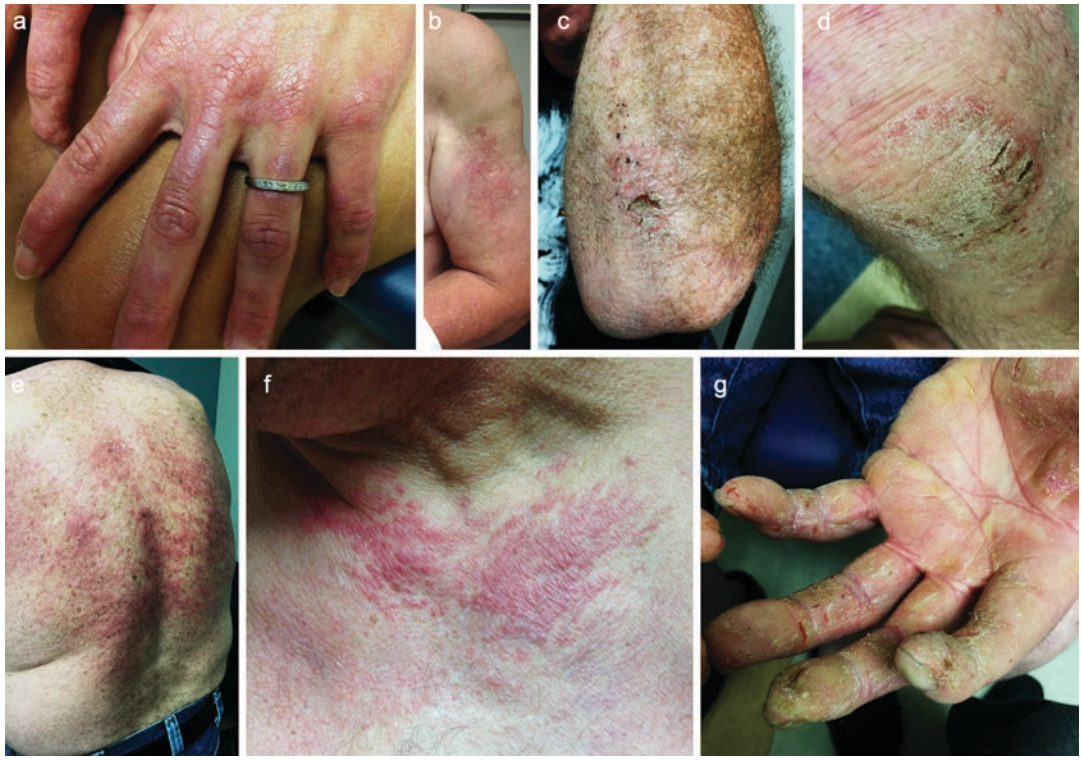

Fig. 20.1 Cutaneous manifestations of immune and inflammatory myopathies (IIM). Gottron's papules (**a**), Gottron's sign, an erythematous rash over extensor surfaces such as elbows (**b**, **c**) or knees (**d**), shawl sign (**e**), V sign (**f**), mechanics hands (**g**)

Antisynthetase Syndromes

Overlap myositis occurs when a patient has an autoimmune myopathy associated with other autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, or systemic sclerosis [35]. Antisynthetase syndrome, with autoantibodies targeting aminoacyl tRNA synthetases, is the most representative form of overlap myositis [36]. Patients may present with a combination of inflammatory myopathy, interstitial lung disease (ILD), arthritis, Raynaud syndrome, fever, or hyperkeratotic finger lesions called mechanic's hands (Fig. 20.1g) [37]. Antisynthetase syndrome may also cause skin rashes similar to dermatomyositis [37]. Myopathic features include proximal weakness similar to DM, although some patients may have no weakness at all and clinical manifestations of muscle disease may be limited to myalgias in isolation.

sIBM

sIBM often presents slowly with progression over 5–8 years before affected patients come to medical attention [18, 38]. Characteristic findings include asymmetric wasting and weakness of the wrist flexors, deep finger flexors, and quadriceps muscles (Fig. 20.2a, b) [24]. Tibialis anterior weakness, dysphagia, and mild facial weakness may also be present [39–42]. In a study of 57 patients with sIBM, the initial presenting symptoms were quadriceps weakness (79%), finger weakness (12%), foot drop (7%), and dysphagia

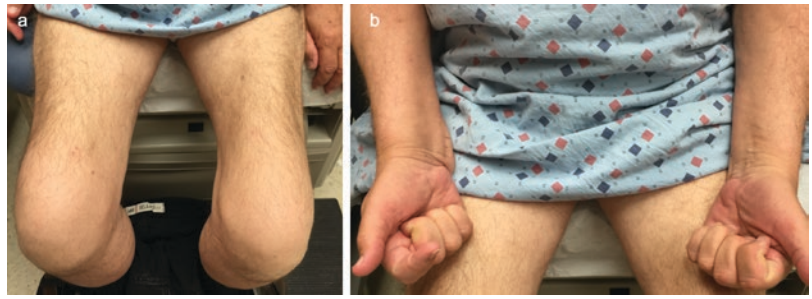

Fig. 20.2 Clinical features of sporadic inclusion body myositis (sIBM). Atrophy and wasting of quadriceps muscles (**a**) and asymmetrical wrist and finger flexor weakness causing impaired ability to make a fist, worse on patient's right side (**b**)

(1.8%) [43]. Asymmetric involvement was very common (82%), with the patient's non-dominant side commonly being more severely affected [43]. There may be evidence of a generalized sensory peripheral neuropathy on clinical exam [44]. Up to 15% of sIBM patients have a coexisting autoimmune disorder or condition with altered immune function [45]. Sporadic IBM is not associated with heart disease [39] or an increased risk of malignancy [46]. Primary respiratory failure is rare; however, progressive dysphagia may occur and may lead to aspiration [40, 41].

Diagnostic Evaluation

Elevated Muscle Enzymes

Serum CK levels are a sensitive measure of muscle disease activity in IIM [24]. They do not correlate well with disease activity when comparing different patients, but they can reflect changes in disease activity within an individual patient. Levels are typically highest in IMNM (2300 U/L–7000 U/L) and lowest in sIBM (160 U/L–793 U/L) [14]. Aldolase levels may also be prominently elevated, presumably from intramuscular connective tissue damage. For example, antisynthetase syndromes with perimysial pathology may have isolated aldolase elevation [42]. Other muscle enzymes, including myoglobin, lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase, may also be elevated. Patients taking hepatotoxic steroid-sparing agents, such as azathioprine (AZA) or methotrexate, may develop elevated transaminases. The liver enzyme gamma-glutamyl transpeptidase (GGT) can aid in differentiating liver damage in IIM patients, as it is not released by damaged muscle [47].

Electrodiagnostics

Electromyography (EMG) typically reveals an irritable myopathic pattern characterized by increased insertional and spontaneous activity (fibrillation potentials, positive sharp waves, and occasionally complex repetitive discharges), polyphasic motor unit action potentials (MUAPs) with small duration and low amplitude, and early MUAP recruitment. sIBM patients may have evidence of neuropathy on nerve conduction studies and mixed myopathic and neurogenic changes on EMG [44].

Muscle Imaging

Muscle MRI in sIBM patients demonstrates severe involvement of the anterior compartment of the thigh and forearm [48]. DM, IMNM, and antisynthetase syndrome patients often have a nonspecific pattern with hyperintensities on intramuscular T2-weighted magnetic resonance imaging (MRI) scans [48, 49]. Some recommend using muscle MRI to select the site of muscle biopsy [50]. Caution should be used with this approach as neurogenic changes from denervation appear similar to changes related to myositis on MRI. MRI also cannot distinguish between IIM and hereditary myopathies [51].

Antibodies

A screen for autoantibodies is common in the evaluation of patients with IIM or suspected IIM. However, their role in the pathophysiology of IIM is unclear. Some may be directly involved in pathophysiology and others simply an epiphenomenon. Antibodies are categorized as myositis-associated autoantibodies (MAAs) or myositis-specific autoantibodies (MSAs). MSAs are found predominantly in the serum of patients with IIM, but are not 100% specific for IIM [52, 53]. MAAs are primarily encountered in other connective tissue diseases and occasionally found in patients with IIM [52, 53]. MSAs can help classify homogenous phenotypic subsets of patients and help predict the degree of muscle, skin, and lung involvement, as well as risk of an associated malignancy (Table 20.1) [14, 29, 32, 33, 41, 52, 54–63]. Recent classification schemes suggest MSAs are crucial for accurate categorization of IIM [14].

Dermatomyositis Approximately 70% of patients with DM have a dermatomyositis-specific autoantibody [52], many associated with a unique clinical phenotype (Table 20.1) [56–61]. Autoantibodies against Mi2, a nuclear antigen, are associated with classic DM characteristics, severe skin manifestations, proximal weakness, and a lower risk of associated malignancy relative to DM associated with other MSAs [56]. DM patients with autoantibodies against nuclear matrix protein NXP2 are more likely to present with both proximal and distal muscle weakness, subcutaneous edema, and dysphagia and are more prone to develop calcinosis [58]. Patients with anti-NXP2 or anti-transcription intermediary factor (TIF)-1 autoantibodies are associated with increased risk of malignancy within 3 years of diagnosis. Accordingly, comprehensive cancer screening or positron emission tomography-computed tomography (PET-CT) scans are particularly important for these patients [57, 58, 64, 65]. DM patients with antibodies against

Table 20.1 Myositis-specific autoantibodies

Myositis-specific autoantibody	Phenotype features
Antisynthetase syndrome	
Anti-histidyl-tRNA synthetase (anti-Jo-1)	90% muscle involvement; 50–75% interstitial lung disease (ILD) [54]
Anti-threonyl-tRNA synthetase (anti-PL-7)	44% muscle involvement; 80% ILD [55]
Anti-alanyl-tRNA synthetase (anti-PL-12)	50% muscle involvement; 90% ILD [54]
Anti-glycyl-tRNA synthetase (anti-EJ)	
Anti-isoleucyl-tRNA synthetase (anti-OJ)	
Anti-asparaginyl-tRNA synthetase (anti-KS)	
Anti-tyrosyl-tRNA synthetase (anti-Ha)	
Anti-phenylalanyl-tRNA synthetase (anti-Zo)	
Dermatomyositis	
Anti-Mi-2	Severe skin manifestations, good response to treatment, less risk of malignancy relative to other forms of dermatomyositis [56]
Anti-transcriptional intermediary factor 1+ (anti-TIF-1)	Adults: Increased risk of malignancy. Children: Severe cutaneous involvement [57]
Anti-nuclear matrix protein 2 (anti-NXP2)	Increased risk of calcinosis. Increased risk of malignancy in adults [57, 58]
Anti-melanoma differentiation-associated protein 5 (anti-MDA5)	Skin ulcerations, palmar papules, and severe ILD syndrome [59, 60]
Anti-small ubiquitin-like modifier 1 (SAE)	Skin manifestations before muscle; dysphagia [61]
Immune-mediated necrotizing myopathy	
Anti-signal recognition particle (anti-SRP)	Severe weakness. Difficult to treat. ILD more common than anti-HMGCR. Onset is most common in autumn [32, 33, 62]
Anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR)	Can cause pure muscle involvement or antisynthetase syndrome-like picture. Increased risk of malignancy vs. anti-signal recognition particle (SRP) [29, 62, 63]

small ubiquitin-like modifier activating enzyme (SAE) or melanoma differentiation-associated gene 5 (MDA5) typically have more cutaneous than muscle involvement [59–61, 66]. MDA5 patients are commonly hypomyopathic or amyopathic and may develop ulcers on the palmar surface of their hands and a rapidly progressive form of ILD [59, 60, 66]. IIM patients suspected to have interstitial lung disease should initially be evaluated and monitored using pulmonary function tests (carbon monoxide diffusion and inspiratory and expiratory pressures) and high-resolution CT scans.

IMNM Several autoantibodies associated with IMNM have been identified, each with specific characteristics and clinical outcomes (Table 20.1) [29, 32, 33, 62, 63]. These include anti-signal recognition particle (SRP) and anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) autoantibodies. Patients with SRP or HMGCR antibodies often share several features, including high CK, and an aggressive refractory disease course in some patients [62]. The IMNM classification does not perfectly overlap with all patients with SRP or HMGCR antibodies. Only two-thirds of IMNM patients are reported to have antibodies to SRP or HMGCR, and around 20% of patients with SRP or HMGCR antibodies do not have key histopathology characteristics of IMNM [33, 63, 67]. Only two-thirds of HMGCR patients have necrosis or regeneration, and one-third have lymphocytic infiltrates [68]. Approximately 60% of these patients will have prominent perimysial pathology, and as high as 37% will have systemic features such as ILD and skin rash, features more commonly seen with overlap or antisynthetase syndromes [68]. The association between statin usage and increased risk of developing IMNM associated with HMGCR antibodies is a subject of ongoing debate [68]. However, it is clear that some patients do have a form of disease triggered by exposure to statins, likely from feedback mechanisms that lead to increased HMGCR expression in muscle tissue [29]. Patients with HMGCR antibodies might have an increased risk of malignancy [69]. Some patients may even present with a slowly progressive disease course and be misdiagnosed with limb-girdle muscular dystrophy [29]. SRP patients tend to have more severe weakness than HMGCR patients [32, 62]. In addition to necrosis and regeneration, SRP muscle pathology demonstrates prominent endomysial fibrosis and capillary pathology [70]. SRP patients may be at greater risk for developing interstitial lung disease and possibly cardiac involvement when compared to patients with HMGCR antibodies [62, 71]. If cardiac involvement is suspected, an electrocardiogram (ECG) and echocardiogram should be performed. Seronegative IMNM is thought to be associated with increased risk of malignancy, female predominance, frequent occurrence of associated connective tissue disorders, and increased risk of extra-muscular disease activity [69, 72].

Antisynthetase Syndrome Autoantibodies against histidyl (anti-Jo-1)-, threonyl (anti-PL7)-, and alanyl (anti-PL12)-tRNA synthetases are the most common [36, 73]. About 90% of patients with anti-Jo-1 autoantibodies have an inflammatory myopathy, while approximately 50% of patients with anti-PL12 autoantibodies present with interstitial lung disease but no muscle involvement [36]. Muscle weakness tends to be more severe in patients with anti-Jo-1 autoantibodies, while lung involvement is more severe in patients with anti-PL7 and anti-PL12 autoantibodies [36, 73].

Sporadic IBM Autoantibodies against cytosolic 5′-nucleotidase 1A (NT5C1A) are present in 30–60% of patients with sIBM. NT5C1A autoantibodies are not specific for sIBM, as they are found in 15–20% of patients with DM, 10% of patients with systemic lupus erythematosus, and 12% of patients with Sjögren's syndrome [74–77]. SIBM patients with NT5C1A antibodies are more commonly female, have greater motor and functional disability, and have more prominent bulbar, facial, and respiratory involvement [78].

Histopathology

Muscle biopsy is a valuable diagnostic tool in patients suspected to have an IIM. The key patho-

logical characteristics of IIM initially recognized by Bohan and Peter criteria were degeneration, regeneration, necrosis, and interstitial mononuclear infiltrates. Inflammatory cell infiltrates are not specific to IIM as they can be seen in muscular dystrophies such as dysferlinopathy, calpainopathy, facioscapulohumeral muscular dystrophy, metabolic myopathies following rhabdomyolysis, granulomatous disorders, myasthenia gravis, vasculitis, and lymphoma, among other disorders [24, 79–84]. Muscle biopsies from patients with DM, IMNM, sIBM, and antisynthetase syndrome are known to have many unique pathological features, suggesting different pathophysiological mechanisms exist for each [8, 82–84]. Each IIM affects specific regions or tissues within skeletal muscle, including connective tissue, blood vessels, and muscle fibers (Fig. 20.3). Pathology can also predict lung involvement, risk of malignancy, and response to immunomodulatory treatment.

Dermatomyositis "Perifascicular atrophy" is the classic feature described in DM (Fig. 20.4a). Some claim this finding is very specific for DM; however, there are several inconsistences [14, 41, 85]. For example, some patients will have prominent perifascicular necrosis instead of atrophy, and others may have minimal inflammatory infiltrates and prominent necrosis similar to IMNM [41, 86]. The classic dermatomyositis clinicopathological picture may therefore be more accurately characterized as dermatomyositis with vascular pathology (DM-VP) [87]. DM-VP biopsies demonstrate a perifascicular myopathy with muscle fiber atrophy, reduced cytochrome oxidase staining, and increased MHC class 1 expression (Fig. 20.4a, b) [8]. The vascular pathology is characterized by abnormal, damaged endomysial capillaries with alkaline phosphatase staining, C5b-9 deposition, and lymphocytic foci surrounding larger vessels in vascular perimysium (Fig. 20.4c, d) [8].

A clinically different subset of patients that are often included under the umbrella categorization of DM have damage to perimysial connective tissue and perifascicular muscle fiber pathology that is often mistaken for DM-VP [8, 88]. Biopsies demonstrate perimysial connective tissue pathology including fragmentation, acid phosphatase-positive histiocytic cells, and alkaline phosphatase staining of the perimysium (Fig. 20.5a–c). Muscle fiber pathology includes necrosis and regeneration, more prominent in

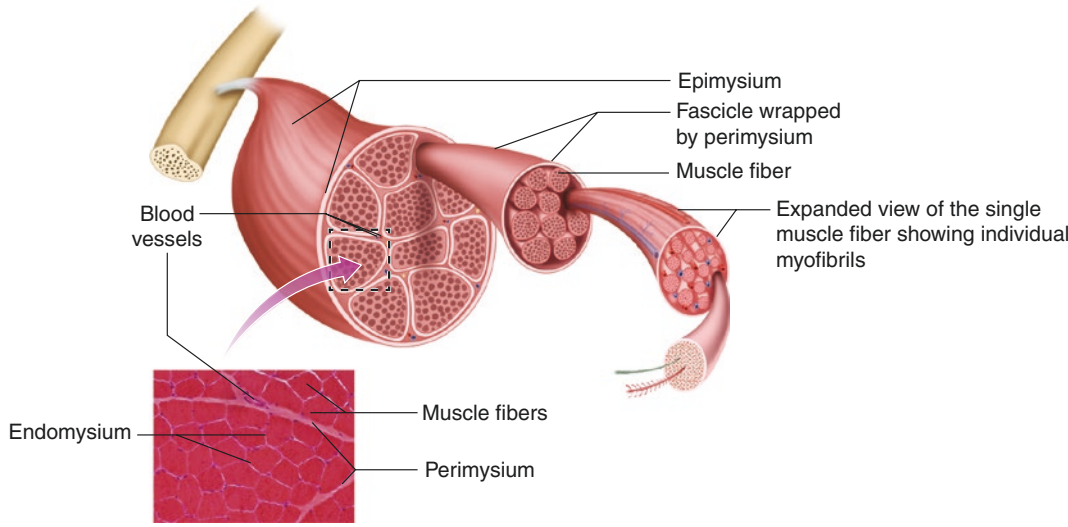

Fig. 20.3 Muscle anatomy. Individual muscle fibers are surrounded by the endomysium, which contains capillaries. Muscle fibers are grouped into fascicles, which are separated by the perimysium. Perimysial connective tissue may contain vasculature. The epimysial connective tissue envelops all fascicles within the muscle

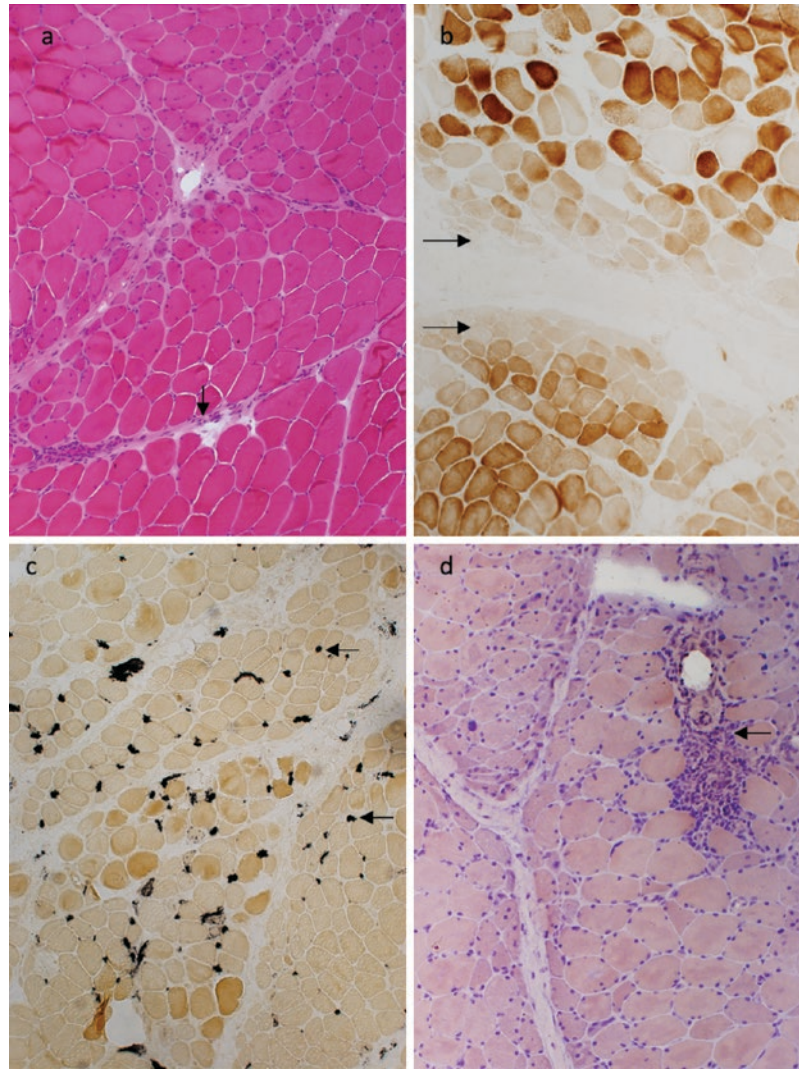

Fig. 20.4 Dermatomyositis with vascular pathology histopathology. H&E demonstrating perifascicular atrophy. Note absence of atrophy adjacent to vascular perimysium (arrow) (**a**). Perifascicular pattern of reduced cytochrome oxidase staining (arrows) (**b**). Alkaline phosphatase highlights enlarged, abnormal endomysial capillaries (**c**). Perivascular lymphocytic infiltrates around intermediate-sized vessels (arrow), distant from muscle fiber atrophy (**d**)

regions neighboring the perimysium (Fig. 20.5d) [8, 88]. These disorders have been termed immune myopathies with perimysial pathology (IMPP) [89]. When compared to DM-VP, IMPP is associated with the clinical picture of antisynthetase syndrome with increased risk of ILD, Raynaud phenomenon, mechanic's hands, inflammatory arthritis, and a higher CK level. IMPP also predicts a sustained response to immunomodulatory therapy and is less frequently associated with a concurrent malignancy [88]. Because of this, IMPP patients require regular screening for ILD. While IMPP patients may have MSAs such as anti-Jo-1 or HMGCR, the large percentage of patients without MSAs emphasizes the important role of myopathology in identifying patients at higher risk of severe comorbid conditions such as ILD.

Regional ischemic immune myopathy (RIIM) is another distinctive pathologic group observed in dermatomyopathy patients and is likely caused by ischemia in border zones between damaged intermediate-sized perimysial blood vessels [90]. Histopathology reveals an unusual pattern of regional muscle fiber necrosis and regeneration with capillary loss in border zones between intermediate-sized perimysial vessels, vascular pathology with damaged walls of intermediate-

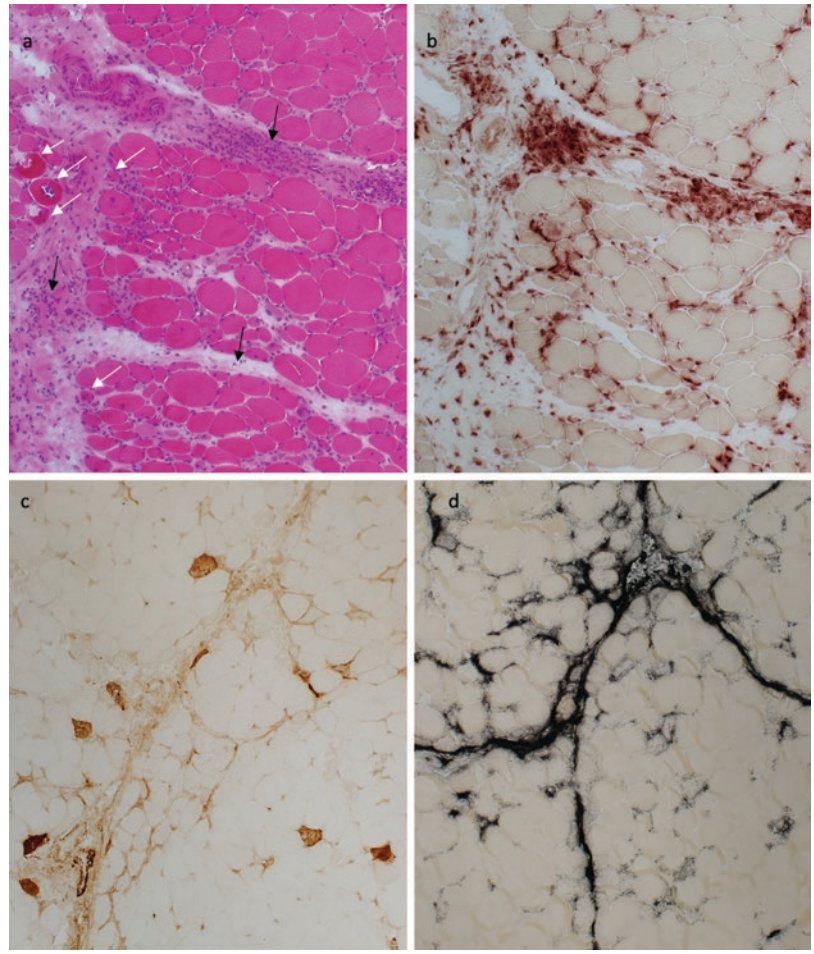

Fig. 20.5 Immune myopathy with perimysial pathology. Perifascicular pattern of necrosis and regenerating fibers (white arrows), with widened, pale, cellular perimysium (dark arrows) (**a**). Acid phosphatase-positive histiocytic cells occupying the perimysium (**b**). Alkaline phosphatase stains the perimysium (**c**). C5b9 stains the perimysium and cytoplasm of necrotic fibers (**d**)

sized perimysial veins, and connective tissue with expression of the ischemia marker carbonic anhydrase IX but no mononuclear inflammatory foci [90].

IMNM The term "necrotizing" may be misleading and imply the whole muscle is necrotic. Immune myopathy "with myofiber necrosis" may be more accurate indicating single myofibers are undergoing necrosis. Regardless, IMNM biopsies typically demonstrate scattered necrotic muscle fibers, although these may be rare or completely absent. Different stages of necrosis/myophagocytosis and regeneration should also be identified [91]. Lymphocytic infiltrates are minimal, if present at all [91]. Sarcolemmal MHC class 1 expression may be seen on non-necrotic and non-regenerating fibers but is often less robust than that seen in other IIMs (Fig. 20.6a–d) [62, 91]. Patchy $C_{5b\text{-}9}$ deposition may be seen. Anti-SRP myopathies more commonly have prominent endomysial fibrosis and enlarged capillaries (Fig. 20.6d–f) [62, 70]. Anti-HMGCR myopathies frequently have perimysial pathology and nuclear abnormalities (Fig. 20.6g–j) [62, 88]. It should be noted that muscle fiber necrosis by itself is not useful for subclassifying IIM [91]. Many different myopathic disorders have prominent muscle fiber necrosis with variable patterns. For example, IMPPs have prominent necrotic fibers near the perimysium [88]. Brachio-cervical inflammatory myopathy has randomly scattered necrotic fibers [92]. Regional ischemic immune myopathy (RIIM) has necrosis of muscle fibers in border zones between vessels [90]. Hereditary and other types of acquired myopathies may also have abundant scattered necrosis.

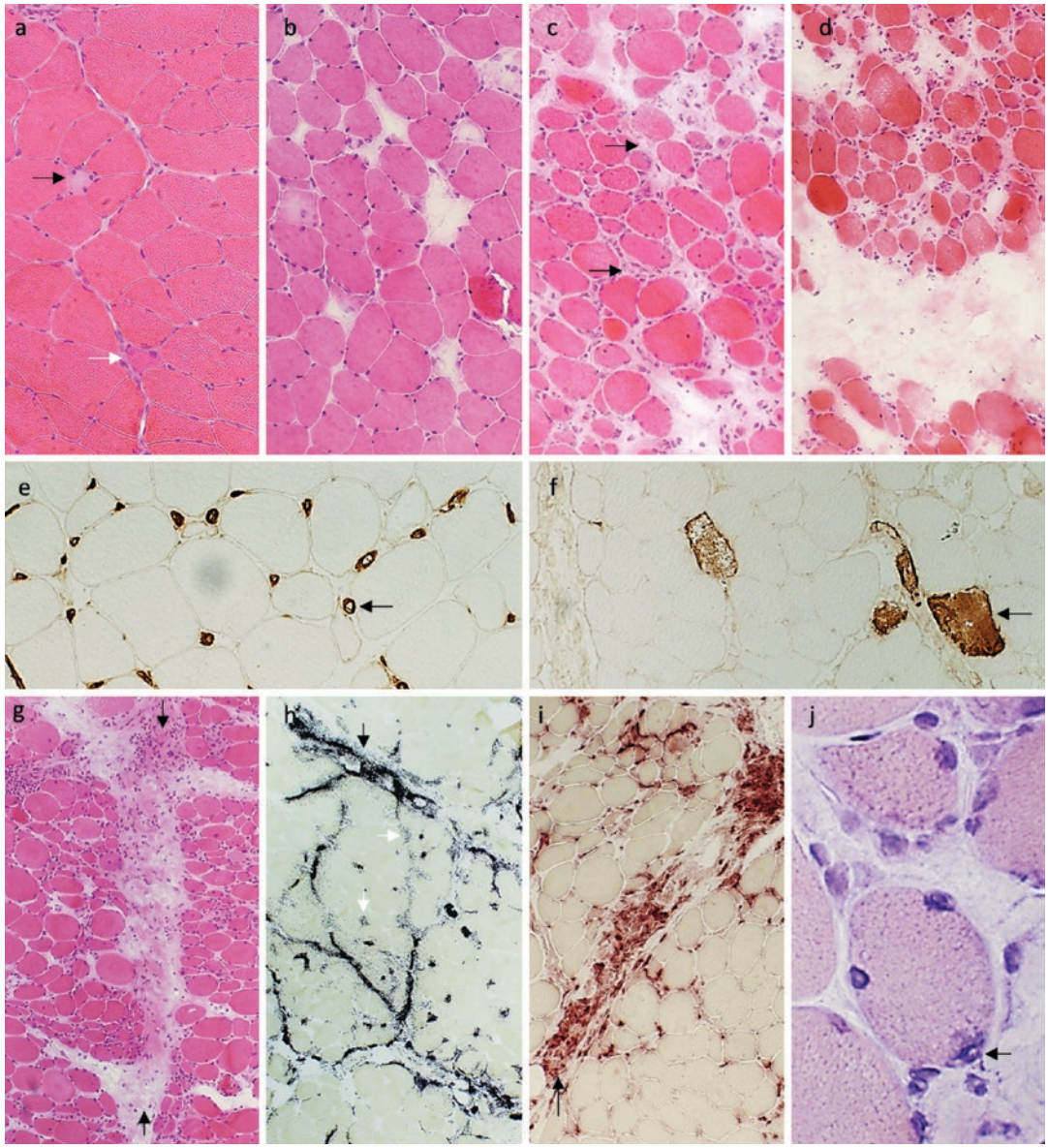

Fig. 20.6 Anti-signal recognition particle (SRP) myopathy and anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) myopathy. Varying degrees of pathology seen in anti-SRP myopathy (**a-d**). Early pathology with scattered necrotic (dark arrow) and regenerating fibers (white arrow) (**a**). Later in disease with mild pathology (**b**), intermediate pathology with moderately increased endomysial connective tissue (arrows) (**c**), and severe pathology with prominently increased connective tissue (**d**). Ulex staining highlights enlarged capillaries (arrow) (**e**). C5b-9 stains the sarcoplasm of necrotic fibers (arrow) (**f**). Anti-HMGCR myopathy more commonly demonstrates immune myopathies with perimysial pathology (IMPP) pathology associated with necrosis. H&E with widened, fragmented, and cellular perimysium with fatty replacement (arrows) (**g**). Alkaline phosphatase highlights the perimysium (dark arrow) and sarcoplasm of immature fibers (white arrows) (**h**). Acid phosphatase highlights histiocytic cells within the perimysium (arrow) (**i**). Congo red staining illustrating nuclear pathology with irregular shapes and clear centers (arrow) (**j**)

Antisynthetase Syndrome Muscle biopsies most commonly demonstrate an IMPP pattern with damaged, fragmented perimysium with adjacent perifascicular myofiber necrosis (Fig. 20.5) [8, 88, 93]. The key clinical difference between DM and antisynthetase syndrome patients with IMPP is simply the presence or absence of antisynthetase autoantibodies [88, 93]. Some antisynthetase syndrome patients may have more widespread necrosis and regeneration [93]. On electron microscopy, nuclear actin aggregation may be seen [94].

Sporadic IBM

Muscle biopsies from patients with sIBM demonstrate a coexistence of mononuclear inflammatory cells and protein aggregation. Specifically pathology reveals an IIM with vacuoles, aggregates, and mitochondrial pathology (Fig. 20.7a–i) [8]. This combination of findings has been abbreviated as IM-VAMP [8]. Atrophic fibers are often grouped and may have a neurogenic appearance [95]. The inflammatory infiltrate is located within the endomysium and composed of CD8 T cells that surround and invade non-necrotic fibers [1, 96]. MHC class 1 is often expressed on the sarcolemma. Vacuoles contain granular basophilic debris and are immuno-reactive for markers of autophagy, amyloid, and aggregation-prone proteins such as TAR DNA-binding protein 43 and phosphorylated neurofilament [1, 8, 97–101]. Aggregates are visualized on H&E as eosinophilic inclusions and may also be highlighted using AMPDA or SMI-31. These tubulo-filamentous inclusions may be seen on electron microscopy and gave rise to the name inclusion body myositis [102].

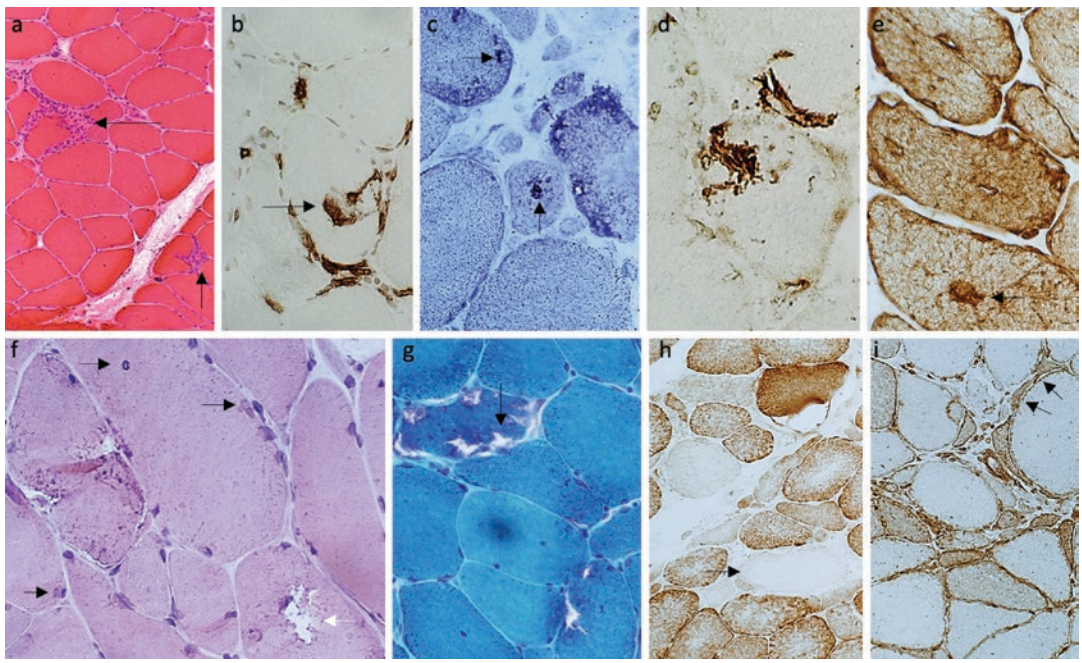

Fig. 20.7 Sporadic inclusion body myositis (sIBM). H&E demonstrating several key features of sIBM including fiber size variability and endomysial inflammatory cell infiltrates invading non-necrotic fibers (arrows) (**a**). Focal invasion of non-necrotic fiber by CD8-positive cells (arrow) (**b**). Aggregates demonstrated by AMPDA (arrows) (**c**), LC-3 (**d**), and desmin staining (arrow) (**e**). Congo red staining illustrating nuclear pathology with clear centers and irregular borders (black arrows) (**f**). Rimmed vacuoles on Congo red staining (white arrow) (**f**) and Gomori trichrome (arrow) (**g**). Cytochrome oxidase-negative fibers (arrow) (**h**). MHC-1 upregulation on sarcolemma (arrows) (**i**)

Mitochondrial pathology manifests as scattered cytochrome oxidase-negative fibers. Abnormal myonuclei are also seen [8, 103]. Muscle from individual sIBM patients may show one or all of these features. Individual muscle fibers typically show only one of these features [8].

Others Many other IIM exist and are not included or well categorized by current classification schemes. These disorders are best understood based on their histopathological patterns.

Routine muscle pathology in brachio-cervical inflammatory myopathy (BCIM, also referred to as B-cell inflammatory myopathy) can be similar to that seen in sIBM with focal invasion by inflammatory cells that are commonly endomysial and perivascular [92]. Perimysial connective tissue staining for alkaline phosphatase; foci of B-cell inflammatory infiltrates (CD20 positive), often associated with ectopic lymphoid structures (ELS); or prominent endomysial C5b-9 complement deposition aid in distinguishing BCIM from other forms of IIM. BCIM syndromes frequently overlap with other immune disorders including myasthenia gravis and rheumatoid arthritis and preferentially involve the proximal arms and posterior neck [92].

Histiocytic inflammatory myopathies have focal collections of cells located in the endomysium or perimysium. Acid phosphatase, esterase, and CD68 stains label cells in the centers of these histiocytic inflammatory foci [8]. In contrast, these stains label only 10–30% of cells in focal mononuclear cell collections. Muscle fiber damage appears as replacement of fibers by histiocytic cells and endomysial connective tissue. The best described histiocytic syndromes are granulomatous myopathies, some of which are associated with sarcoidosis [8, 104]. Histiocytic foci and granulomas in muscle can occur without myopathy in systemic sarcoidosis or vasculitic lesions [8, 104]. Collections of histiocytic cells are also found in macrophagic myofasciitis (MMF) and inflammatory myopathy with abundant macrophages (IMAMs) [8, 105–107]. MMF and IMAM may be related to immunizations and be clinically silent [108]. Therefore, identifying IMAM histiocytic cell collections should not preclude further search for alternative causes of weakness.

Pathogenesis

The clinical and histopathological distinctions between IIMs suggest different pathogenic processes underlie each, but the precise mechanisms leading to tissue injury are poorly defined.

Dermatomyositis The precise mechanisms responsible for DM are unknown. Several different DM models have been proposed. One model focuses on a central role for type 1 interferons (IFN) causing capillary, myofiber, and connective tissue injury [109–111]. Alternatively, DM myofiber injury may result from an antibody and complement-mediated microangiopathy [8, 112, 113], and the resulting hypoxia triggers IFN production [114]. The pathogenic role of myositis-specific autoantibodies in DM is uncertain [11, 41]. DM in some patients is a paraneoplastic syndrome associated with cancer through unknown mechanisms. Future studies of DM pathogenesis should avoid lumping together distinct clinicopathological groups (DM-VP, IMPP, RIIM), which likely have different pathomechanisms.

A combination of genetic risk factors and exposure to environmental factors may be required to trigger DM. Certain class 2 HLA alleles have been implicated in dermatomyositis pathogenesis [115]. Exposure to ultraviolet light is also a known risk factor for developing dermatomyositis [116]. However, the majority of people with known genetic risk factors and high ultraviolet light exposure never develop DM. Mutations in *TIF1* genes in tumors from patients with DM positive for anti-TIF1 autoantibodies have been reported [117]. Once a patient has developed DM, it is unclear what mechanisms maintain muscle damage and weakness.

IMNM The mechanisms underlying this condition are unknown. Despite the lack of substantial immune cell invasion of muscle, this condition

can respond to immunosuppressive therapies, suggesting it is immune-mediated. While statins are known to cause rhabdomyolysis, their association with anti-HMGCR myopathy is not clear, and the condition should not be called a statin myopathy [29, 68]. That stated, there is evidence that HMGCR is expressed by muscle fibers, particularly regenerating fibers, and that antigen expression is increased by statin exposure (via feedback mechanisms similar to those present in hepatocytes) [29]. Accordingly, in patients with anti-HMGCR antibodies, exposure to statins could lead to increased antigen expression and further, immune-mediated, muscle damage. Class 2 HLA-allele DRB1*08:03 is associated with anti-SRP myopathy, and DRB1*11:01 is an immunogenic risk factor for anti-HMGCR myopathy [118]. Some have proposed anti-SRP and anti-HMGCR antibodies are directly pathogenic [67]; however, these antibodies were unable to induce necrosis in vitro [119], indicating further studies are required.

Antisynthetase Syndrome Little is known about what triggers and maintains autoimmunity in antisynthetase syndrome. A pathogenic role for these antibodies remains unproven. Mouse models of myositis induced by immunization with histidyl-tRNA synthetase are not dependent on the development of antibody responses [120]. Instead, they are thought to be mediated by innate immune mechanisms or by the action of histidyl-tRNA synthetase as a chemokine [120].

Sporadic IBM Pathologic features of sIBM can be divided into two categories: inflammatory changes and myodegenerative pathologies [8]. These two pathologies have led to pathomechanistic speculation as to whether sIBM is a primary inflammatory, or a primary degenerative, myopathy.

Several lines of evidence suggest that unlike other IIM, sIBM is a primary degenerative myopathy. Rimmed vacuoles are immuno-reactive for autophagic markers such as LC3 suggesting they are autophagic in origin [97–100]. Inclusions are also immuno-reactive for aggregate-prone proteins including amyloid precursor protein, phosphorylated neurofilament, and TDP-43 [99, 121–124]. Rimmed vacuoles may also be found in hereditary inclusion body myopathies or protein aggregate myopathies. Dominantly inherited mutations in the ubiquitin adaptor valosin containing protein (VCP) cause a multisystem degenerative syndrome manifesting with IBM, Paget's disease of bone (PDB), motor neuron disease, and fronto-temporal dementia [125]. Rare variants in SQSTM1 have also been identified in patients with a similar phenotype [126]. Both SQSTM1 and VCP accumulate in sIBM patient muscle, often within or adjacent to rimmed vacuoles [100, 125]. FYCO1, similar to SQSTM1, is an autophagic adaptor protein that binds autophagosomes and facilitates their maturation to acidic lysosomes along microtubules [127]. FYCO1 is a strong marker of rimmed vacuoles, and disease-associated variants impair autophagosome binding in skeletal muscle suggesting they may disrupt autophagic degradation [128]. FYCO1 variants are statistically overrepresented in sIBM patients compared to controls and may serve as risk alleles [128]. These studies support that the degeneration in sIBM patient muscle may be due to a more global disruption in protein degradation pathways, and future treatment strategies aimed at improving protein degradation or protein aggregates may be therapeutic for sIBM. As proof of concept, mice expressing pathogenic VCP mutations were treated with a small molecule, arimoclomol, that enhances the heat shock response. This causes a coordinated upregulation of protein chaperones to facilitate proper folding or degradation of misfolded proteins [129]. Arimoclomol reduced both ubiquitin and TDP-43 pathology and increased forelimb grip strength. These data were supported by a phase II clinical trial in 16 sIBM patients [129].

A number of observations have also strongly implicated autoimmunity as a central pathologic mechanism in sIBM. For example, the invasion of myofibers by cytotoxic CD8+ T cells is a prominent feature in muscle biopsies from sIBM patients [96, 130, 131]. Both oligoclonal and polyclonal expansions of T cells exist within

muscle from sIBM patients and support the idea that there is a continuous antigen-driven inflammatory process in sIBM [132]. Many sIBM patients have abnormal clonal expansions of circulating granular lymphocytes that express CD57, a marker of persistent antigenic stimulation that defines a population of T cells with increased cytotoxic potential and resistance to apoptosis [133]. In fact, most sIBM patients meet criteria for T-cell large granular lymphocytic leukemia (T-LGL) [133]. In sIBM, muscle is invaded by the CD8+ CD57+ lymphocytes, which contain cytotoxic granules, analogous to T-LGL where these same cells invade the bone marrow, spleen, and liver. These findings suggest persistent antigenic stimulation of T cells precipitates a neoplastic-like disorder, with cytotoxic T cells invading muscle and circulating in the blood [134].

Dense inflammatory collections consistent with ELS have also been identified in sIBM muscle [135]. Clonally related B cells and plasma cells within these intramuscular lymphoid structures suggest antigen-stimulated maturation of antibody-producing plasma cells occurs locally within sIBM muscle. These findings led to the discovery of autoantibodies targeting cytosolic 5′-nucleotidase 1A (NT5C1A) [136, 137], an enzyme that catalyzes the hydrolysis of adenosine monophosphate to adenosine and inorganic phosphate. NT5C1A is aberrantly localized to perinuclear regions and vacuole rims in sIBM skeletal muscle cells [138]. Whether the abnormal distribution of NT5C1A plays a role in triggering an autoimmune response in sIBM has not been determined.

Another interesting point regarding sIBM pathogenesis is the sIBM-like syndrome that develops in human immunodeficiency virus (HIV)-positive patients. Initially these patients may present, at a younger age of onset, with very high CK levels and proximal weakness that may improve with treatment. However, all patients eventually develop features most consistent with inclusion body myositis, including finger and wrist flexor weakness, rimmed vacuoles, or anti-NT5C1A autoantibodies [139].

Classification

There have been many attempts to establish classification and diagnostic criteria for IIMs. Bohan and Peter proposed their system to establish clear guidelines for diagnosis and classification of PM and DM [140]. These criteria are too inclusive, allowing patients with various muscular dystrophies to be diagnosed with IIM [79], and they are unable to distinguish sIBM, IMNM, antisynthetase syndrome, and DM. Many other classification schemes have been proposed, all attempting to improve the homogeneity of diagnostic categories, so treatment and prognosis may be evaluated accurately. No universally accepted classification system currently exists. IIMs such as BCIM, focal myositis, and others are distinct and well characterized clinically and pathologically, yet are not recognized by current classification schemes [92, 141, 142].

Clinical-serologic associations have helped to more accurately categorize patients and predict risk of malignancy or ILD; however, the utility of classification schemes based on MSAs is limited [10]. Many MSAs lack specificity for a distinct syndrome [14, 52, 53]. MSAs also lack sensitivity as many IIM patients are seronegative [14, 52, 53].

Other classification schemes have placed more emphasis on muscle pathology and facilitated the initial distinction between sIBM and PM [22, 143]. The importance of histopathologic criteria was demonstrated by a retrospective follow-up study of 165 IIM patients that suggested the diagnosis of PM is rare and actually includes a heterogeneous group of disorders [4].

In 2003, two new distinct pathologic entities were proposed at a consensus conference of the European Neuromuscular Centre (ENMC), IMNM and nonspecific myositis, which included patients with nonspecific perimysial/perivascular infiltrates, but without biopsy features diagnostic of DM or PM [144]. In 2011, another classification system was proposed based solely on myopathology that avoided inconsistencies of other clinical classification systems [8]. It utilizes pathologic characteris-

tics, types of muscle fiber damage, and tissues involved to subclassify IIMs. It defined six new pathologic classes: IMPP (seen in antisynthetase syndrome or "DM" cases with ILD), myovasculopathies (seen in dermatomyopathies such as DM-VP and RIIM), immune polymyopathies (such as anti-SRP and HMGCR myopathies), immune myopathies with endomysial pathology (seen in BCIM), histiocytic inflammatory myopathy (seen in granulomatous disorders, MMF, and IMAM), and IM-VAMP (seen in sIBM) [8, 68, 70, 87–90, 92, 99, 104].

While this system provides consistent and inclusive classification, such specialized myopathological techniques are not widely available. In addition, accurate interpretation of specimens is also problematic [14]. This is evident in the most recent classification scheme, which proposes using only clinical findings and MSAs while excluding histopathology [14]. They note this system may be used to determine what type of IIM a patient has, not if a patient has IIM. Based on phenotypic, biological, and immunologic data, four clusters (DM, IBM, IMNM, antisynthetase syndrome) were identified. They developed a simplified decisional tree with 78.4% correct estimation of their self-defined clusters using three variables: DM rash, antisynthetase syndrome antibodies, and finger flexor scores of 3 or less on the Medical Research Council (MRC) scale [14]. Many problems result from this oversimplification. By ignoring histopathology, many antisynthetase antibody-negative patients are miscategorized. This includes seronegative IMPP patients who are still at increased risk of ILD [88]. This scheme also improperly classifies 35% of sIBM patients as IMNM and 8.7% of IMNM patients as sIBM [14]. This leads to a very problematic situation of incorrectly initiating or withholding immunosuppression in the setting of not having a biopsy to guide further management. While many aspects of these criteria are not ideal, they have been useful in eliminating polymyositis as a diagnostic entity.

Treatment

Treatment for IIMs remains challenging. The absence of standardized treatment guidelines is reflective of their low prevalence, phenotypic heterogeneity, and suboptimal classification systems. Currently, treatment requires a multidisciplinary approach managed by experienced clinicians.

IIMs Other Than sIBM The shortage of adequate randomized trials has resulted in treatment strategies relying on historical clinical practice, case series, and expert opinion.

Glucocorticoids are first-line treatment, but side effects (weight gain, osteoporosis, hypertension, diabetes) limit their use as a monotherapy. At initial presentation, intravenous methylprednisolone (IVMP) is typically given at 1 gram daily for 3–5 days depending on severity. More conservative approaches will initiate prednisone at starting doses of 0.5–1 mg/kg/day at a maximum of 100 mg/day. Some will maintain daily prednisone for 4–6 weeks and then taper. We utilize pulse dose steroids to minimize side effects [145–147], starting at 1 gram/week for 1–2 months, followed by 1 gram every 2 weeks for another 1–2 months, at which time patients are reassessed. Further tapering is facilitated by slowly increasing time between doses or reducing total dose and guided by repeat clinical examinations.

Other immunosuppressive and immunomodulatory drugs commonly used for IIMs include methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, intravenous immunoglobulin (IVIg), rituximab, and cyclophosphamide (Table 20.2). Certain clinical settings guide the selection of different drugs. Methotrexate is useful as a steroid-sparing agent for muscle and joint disease when relatively quick onset (months) is desired, but may cause lung toxicity and should be avoided in patients with ILD [148]. Azathioprine is useful in patients

Table 20.2 Immunomodulatory treatments for immune and inflammatory myopathies (IIM)

Drug	Indications	Dose	Side effects	Monitoring
Corticosteroids	Severe cases, all manifestations	1 g/day for 3–5 d and then daily prednisone or intermittent dosing: 1 g/week for 1 month, 1 g/every other week for 2 months. Taper further via slow dose or frequency reduction	Hypertension, weight gain, hyperglycemia, osteoporosis, cataracts, infection, insomnia	Weight, blood pressure, serum glucose, bone density, cataracts
	All patients, all manifestations	Daily: 0.5–1 mg/kg/day. Intermittent: 3.5–7 mg/kg/week. Taper: After 3–6 months or clinical improvement. Reduce by 5 mg every 2–6 weeks		
Azathioprine	Steroid sparing. Muscle involvement	2–3 mg/kg/day	Myelosuppression, hepatotoxicity, malignancy, teratogenicity, alopecia, flu-like hypersensitivity reaction	Thiopurine methyltransferase enzyme activity before initiation, CBC, and CMP
Methotrexate	Steroid sparing. Muscle involvement. Avoid in ILD	7.5 mg/week for 2 weeks, titrate to maximum 25 mg/week in 2.5 mg increments IM/SQ administration may have more efficacy than PO	Hepatotoxicity, myelosuppression, alopecia, pneumonitis, teratogenicity, malignancy, renal insufficiency	Weekly CBC and CMP for 1 month, monthly for 6 months, every 3 months thereafter
Cyclosporine	Steroid sparing. Skin involvement and ILD	3–5 mg/kg/day	Hypertension, nephrotoxicity, hepatotoxicity, myelosuppression	Blood pressure, CBC, CMP, cyclosporine troughs with goal 50–150 ng/ml
Tacrolimus	Steroid sparing. ILD	0.06 mg/kg/day	Hypertension, hepatotoxicity, nephrotoxicity, hirsutism, tremor, teratogenicity	Blood pressure, CMP, tacrolimus troughs with goal 2–9 ng/ml
Mycophenolate mofetil	ILD	2–3 g/day in divided doses	Myelosuppression, nausea, diarrhea, hypertension	Blood pressure, CBC
Cyclophosphamide	ILD	IV: 0.7–1 g/M^2 for 1 d/month for 5–6 months Oral: 10–15 mg/kg per month for 6–12 months	Vomiting, alopecia, hemorrhagic cystitis, myelosuppression, malignancy, infertility	Urinalysis, monthly CBC
IVIg	Dysphagia and severe disease refractory to other treatments	2 g/kg over 2–5 days and then 0.4–2 g/kg every 4–6 weeks	Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, aseptic meningitis, anaphylaxis, thrombosis	Heart rate, blood pressure, kidney function
Rituximab	Severe IIM, rapidly progressive ILD	375 mg/M^2 weekly for 2 weeks and then every 10 weeks for 2 years	Infusion reaction, infection, progressive multifocal leukoencephalopathy	CD19 count, quantitative immunoglobulins, CBC, and BMP

CBC complete blood count, *CMP* comprehensive metabolic panel, *ILD* interstitial lung disease, *IM* intramuscular, *SQ* subcutaneous, *PO* per oral, *IV* intravenous, *IVIg* intravenous immunoglobulin, *BMP* basic metabolic panel

with normal thiopurine methyltransferase activity for long-term immunosuppression when rapid onset is not necessary [149]. Mycophenolate mofetil, cyclosporine, and tacrolimus may be useful for ILD refractory to corticosteroids [150–152]. Cyclosporine and tacrolimus have been used for skin manifestations in DM [150, 151]. Cyclophosphamide may be used in patients with more severe ILD who do not respond to steroids; however, it is associated with more adverse events including infertility [153]. IVIg has shown efficacy in a randomized controlled trial and in a retrospective study for the management of dermatomyositis [154, 155]. IVIg and methotrexate are also effective for anti-HMGCR myopathy [91, 156]. Subcutaneous immunoglobulins (SCIg) may be an alternative to intravenous administration, but reports of SCIg use in IIM are quite limited. Rituximab, a monoclonal antibody targeting CD20 on B lymphocytes, was assessed in refractory DM and polymyositis [157]. While the rituximab arm of this study failed to meet the investigator defined primary endpoint, there were clear benefits to rituximab use in this patient population in that 83% of subjects receiving rituximab met the trial definition of improvement, a criteria generated from measures including muscle strength, muscle enzyme testing, and qualitative disease severity scales [157]. It also appears to be efficacious in patients with antisynthetase syndrome, with or without ILD, and in patients with anti-Mi2, anti-SRP, and anti-HMGCR antibodies [32, 91, 158].

The treatment strategy for juvenile DM is similar to adults [159]. The initial prednisone dose is 2 mg/kg, and methotrexate is the main steroid-sparing agent, although azathioprine, cyclosporine, and tacrolimus have been used. IVIg is the preferred agent for refractory cases. Rituximab is increasingly utilized, and cyclophosphamide is used for severe or life-threatening cases [159].

Evidence is conflicting regarding the use of anti-tumor necrosis factor agents in IIM [160–162]. In fact, exposure to anti-TNF drugs has been reported as a precipitant for IIMs in the literature. Abatacept, a fusion protein that inhibits T-cell co-stimulation, showed benefit by reducing disease activity in a pilot study of 20 IIM patients [163]. Case reports have noted efficacy in IIM for tofacitinib [164] and ruxolitinib (Janus kinase inhibitors) [165], tocilizumab (IL-6 antagonist) [166], anakinra (IL-1 antagonist) [167], and alemtuzumab (anti-CD52) [168]; however, confirmatory studies are required.

Sporadic IBM In contrast to other IIMs, no pharmacological therapy has been shown to be effective for sIBM. Treatment of this form of myositis remains largely supportive. Immunosuppressive drugs, such as corticosteroids, azathioprine, methotrexate, or etanercept, have not shown efficacy in sIBM [134, 169]. Alemtuzumab showed a trend toward a reduction of biomarkers in a pilot study that was not confirmed in a subsequent study [170]. Bimagrumab [171] (a monoclonal antibody that blocks the myostatin pathway) and follistatin [172] (myostatin inhibitor locally delivered using an adeno-associated virus) improved thigh muscle volume and performance on the 6-minute walk test but did not significantly improve muscle strength. Rapamycin, also known as sirolimus, improved performance on the 6-minute walk test but did not improve quadriceps strength [173]. Oxandrolone and simvastatin were also not effective [174, 175]. A randomized controlled trial (NCT02483845) investigating natalizumab, an FDA-approved therapy for multiple sclerosis that prevents T-cell egression out of vasculature, is ongoing. A large randomized controlled trial of arimoclomol is ongoing (NCT02753530).

Management

Physical Exercise Physical exercise and rehabilitation programs under the supervision of a physical therapist are safe in all types of IIM and are generally recommended to increase strength and reduce disability [176, 177].

Skin Disease Patients with skin manifestations should use sunscreen and avoid UV rays. Topical steroids and tacrolimus have been used [178]. Hydroxychloroquine, an antimalarial drug, also is also commonly used for cutaneous manifestations.

Calcinosis Calcinosis commonly fails to respond to immunosuppressive and immunomodulatory therapies. Diltiazem may help [179]. Abatacept and sodium thiosulfate, a calcium chelator, improved calcinosis in a case report [180]. Surgical excision is an option [159].

Dysphagia Dysphagia may occur in all subtypes of IIM and is particularly common in sIBM. IVIg may improve swallowing in sIBM and other forms of IIM [181–183]. Cricopharyngeomyotomy, pharyngoesophageal dilation, and injection of botulinum toxin may be used when dysphagia results from failure of upper esophageal sphincter relaxation [184–186].

Treatment of Associated ILD Patients with even mild ILD should be intensively treated from onset with glucocorticoids and a second-line immunosuppressant agent (tacrolimus or mycophenolate mofetil). When ILD progression is detected, immediate, intensive treatment should be initiated. This includes methylprednisolone pulses along with a second-line immunosuppressant (tacrolimus, cyclophosphamide, or rituximab). Other treatments to consider include two courses of polymyxin in 24 hours, daily plasmapheresis for 3 days followed by every other day for a total of seven sessions, and IVIg after each plasmapheresis session [41, 187, 188]. Lung transplantation may be considered as a last-resort treatment [188].

Conclusions and Future Directions

Currently, four main types of inflammatory myopathies are recognized: dermatomyositis, immune-mediated necrotizing myopathy, sporadic inclusion body myositis, and antisynthetase syndrome. The ongoing controversy regarding classification of IIMs will likely only be resolved through a deeper understanding of pathogenesis. Improved alignment of clinical, laboratory, and histopathologic data will facilitate the development of more efficacious treatments.

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