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20–21-gauge needle prick. It is rather unique for Behçet syndrome and is part of the ISG diagnostic criteria. Arthralgia or arthritis is seen in about half of patients; it is usually a mono- or oligoarthritis in the lower extremities and does not usually cause erosions or deformity. Eye involvement is seen in half of all patients and may be seen in up to ~70% of males. It is most commonly a bilateral panuveitis. A hypopyon, seen in ~10% of patients with eye disease, is an intense inflammation in the anterior chamber and is quite specific for Behçet syndrome. Ocular involvement develops usually in the first 2 years after fulfillment of diagnostic criteria and is most severe during the first few years and then tends to abate. Male gender, posterior involvement, frequent attacks (>3 per year), strong vitreous opacity, and macular edema are poor prognostic factors. Vascular disease is seen in up to 40% of patients. It is associated with intensive thrombosis and runs a relapsing course. Several welldefined venous vascular associations are seen; superficial and deepvein thrombosis, Budd-Chiari syndrome, inferior vena cava syndrome, pulmonary artery involvement, intracardiac thrombosis, and cerebral venous sinus thrombosis frequently cluster in various combinations. Pulmonary artery aneurysms carry a 5-year mortality rate of 20–25%. Prevalence of neurologic involvement is ~5%, with about threequarters of patients presenting with parenchymal involvement, while the remaining cases present with cerebral venous sinus thrombosis. These two forms rarely occur together. Parenchymal involvement usu ally affects the telencephalic-diencephalic junction, brainstem, and spinal cord. Patients may present with a subacute onset of severe head ache, cranial nerve palsy, dysarthria, ataxia, and hemiparesis. Prevalence of gastrointestinal involvement changes significantly across different populations (up to 50% in the Far East but rare in the Middle East). Clinical and endoscopic appearance of intestinal involve ment can be similar to, and thus cannot easily be differentiated from, Crohn’s disease. Ulcers tend to be single or less than five, are usually confined to the ileocecal area, are more likely to be deep and round, and are prone to perforate; perianal and rectal area involvement are rare. In practice, it is difficult to distinguish Behçet syndrome from Crohn’s disease unless extraintestinal manifestations are present. TREATMENT Behçet Syndrome Treatment is guided by type and severity of involvement, with the goal of preventing long-term damage. Most new manifestations tend to present within the first 5 years, and for most patients, the natural course is one of diminishing symptoms culminating in potential remission, frequently not requiring ongoing treatment with medications. Patient characteristics, such as being young and male, need to be kept in mind when making treatment decisions, as these patients tend to have a worse prognosis. In most patients, tapering and/or stopping their medications in 2–3 years after the symptoms have improved should

be attempted. Oral ulcers can be managed with topical glucocorticoids and on an as-needed basis if mild. Lesions resistant to local measures may require systemic treatment with colchicine, oral glucocorti coids, immunosuppressants such as apremilast, azathioprine, or a tumor necrosis factor (TNF)-α inhibitor such as infliximab. A similar treatment approach can be used for genital ulcers and other mucocutaneous manifestations. Patients may need a combination of medications, at least initially, to control disease activity. Eye involvement, given its frequency and potential morbid ity, requires early and aggressive treatment with brief courses of glucocorticoids and longer-term treatment with an immunosup pressant. Azathioprine is usually the preferred agent in clinical practice. TNF inhibitors infliximab or adalimumab can also be used, either as first-line monotherapy or more commonly in com bination with systemic glucocorticoids and azathioprine, for control of disease activity. Cyclosporine can also be considered in combi nation regimens; monotherapy with interferon is another option.

Glucocorticoids can be tapered in many patients after active disease has been controlled, whereas immunosuppressants are generally continued for at least 2 years with plans to potentially taper them also based on treatment response and ongoing disease activity.

Gastrointestinal involvement is treated with glucocorticoids plus an immunosuppressant such as azathioprine alone or in combina tion with infliximab. CHAPTER 377 Venous thrombotic events are treated by controlling systemic inflammation with immunosuppressive medications (usually azathio prine or, for more severe cases, cyclophosphamide), rather than using anticoagulants. However, if venous thrombotic events occur, standard anticoagulation treatment can be given, provided there is a low risk of bleeding and there are no coexistent pulmonary artery aneurysms. For central nervous system involvement, the combina tion of azathioprine and a TNF inhibitor is usually the first choice. Inflammatory Myopathies ■ ■FURTHER READING Hatemi G et al: 2018 update of the EULAR recommendations for the management of Behçet’s syndrome. Ann Rheum Dis 77:808, 2018. Kural-Seyahi E et al: The long-term mortality and morbidity of Behçet syndrome: A 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore) 82:60, 2003. Yazici H et al: Behçet syndrome: A contemporary view. Nat Rev Rheumatol 14:107, 2018. Yazici Y et al: Behçet syndrome. Nat Rev Dis Primers 7:67, 2021. Steven A. Greenberg, Anthony A. Amato

Inflammatory

Myopathies This chapter focuses on the major types of inflammatory myopathies (IMs), including dermatomyositis (DM), polymyositis (PM), immunemediated necrotizing myopathy (IMNM), antisynthetase syndrome (ASyS), and inclusion body myositis (IBM) (Table 377-1). Other IMs include those caused by infection, eosinophilic myositis, granuloma tous myositis, and myositis triggered by checkpoint inhibitors. Of note, inflammatory cell infiltrates can also be occasionally seen in muscle biopsies of hereditary myopathies (e.g., muscular dystrophies, meta bolic myopathies), sporadic late-onset nemaline myopathy (SLONM), and toxic myopathies. Epidemiologic studies suggest that the incidence of IM grouped together is up to 16 cases per 100,000 with prevalence in the range of 14–32 per 100,000. Defining the actual incidence and prevalence of the individual myositides is limited, however, by different diagnostic criteria employed in various epidemiologic studies, an increasing rec ognition of ASyS and IMNM, as well as the frequent misdiagnosis of IBM. Idiopathic PM without signs of an overlap syndrome is quite rare

compared to DM, ASyS, IBM, and IMNM that occur in roughly simi lar frequencies. DM can occur in children (juvenile DM), while IBM always occurs in adults and is the most common cause of myopathy in those aged >50. DM, PM, and ASyS are more common in women, while IBM is more common in men. DIAGNOSTIC APPROACH AND DIFFERENTIAL DIAGNOSIS The approach to patients with suspected myopathy is detailed in Chap. 460. In any patient presenting with weakness, the first step is to localize the site of the lesion by history and clinical findings (Chap. 26). Weakness could be caused by a process in the cerebral hemispheres, spi nal cord (Chap. 453), anterior horn cell (Chap. 448), peripheral nerve

TABLE 377-1 Inflammatory Myopathies: Clinical and Laboratory Features AGE OF ONSET RASH PATTERN OF WEAKNESS LABORATORY FEATURES MUSCLE BIOPSY DISORDER SEX DM F > M Childhood and adult Yes Proximal > distal Normal or increased CK (up to 50× normal or higher); various MSAs (anti-MDA5, anti-TIF1, anti-Mi-2, anti-NXP2) PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders PM F > M Adult No Proximal > distal Increased CK (up to 50× normal or higher) IMNM M = F Children and adults No Proximal > distal Elevated CK (>10× normal or higher); anti-HMGCR or antiSRP antibodies ASyS F > M Children and adults Sometimes Proximal > distal Elevated CK (>10× normal or higher); antisynthetase antibodies IBM M > F Older adults (>50 years) No Proximal and distal; predilection for: finger/ wrist flexors, knee extensors Normal or mildly increased CK (usually <10× normal); anticN-1A antibodies; large granular lymphocytes on flow cytometry and reduced CD4/CD8 ratio with increased CD8 count Abbreviations: CK, creatine kinase; cN-1A, cytosolic 5′-nucleotidase 1A; CTDs, connective tissue diseases; COX, cytochrome oxidase; DM, dermatomyositis; F, female; g, immunoglobulin; IBM, inclusion body myositis; IFN-1, type 1 interferon; ILD, interstitial lung disease; IS, immunosuppressive; M, male; MAC, membrane attack complex; MDA5, melanoma differentiation antigen; MHC-1, major histocompatibility antigen 1; MSA, myositis-specific autoantibodies; NCP2, nuclear matrix protein 2 (NXP2); NM, necrotizing myopathy; PM, polymyositis; TIF1, transcriptional intermediary factor 1. Source: Reproduced with permission from AA Amato, JA Russell (eds): Neuromuscular Disorders. 2nd ed. New York: McGraw-Hill Education; 2016. (Chaps. 457–458), neuromuscular junction (Chap. 459), or muscle (Chap. 460). Past medical history, medication use, and family history, combined with a detailed clinical examination and an appreciation for the pattern of muscle involvement (e.g., what muscles are weak and atrophic or hypertrophic as well as the presence of scapular winging, early contractures, sensory abnormalities, fasciculations, or rash), help differentiate myopathies from other neuromuscular disorders and the different types of myopathies from each other (see Chap. 460). For example, atrophy with fasciculations suggests a neurogenic process such as amyotrophic lateral sclerosis, fatigable weakness on examination points to a neuromuscular junction defect such as myasthenia gravis, and concomitant sensory symptoms suggest a central process such as a spinal cord disorder or a polyneuropathy. Scapular winging, calf hypertrophy or atrophy, and early contractures before significant weak ness develops would strongly suggest a muscular dystrophy, particularly if there is a positive family history. A heliotrope rash combined with Gottron papules (below) and dilated nailfold capillaries is diagnostic for DM. The presence of atrophy and weakness of the flexor forearm muscles and quadriceps in a person aged >50 years is most likely IBM. When the site of the lesion cannot be localized based on history and clinical examination alone, laboratory testing is required. Serum creatine kinase (CK) is the most sensitive laboratory marker of muscle destruction. Not all myopathies are associated with elevated CK levels, but a markedly elevated CK (e.g., >2000 U/L) is almost always due to a myopathy. A slightly elevated CK can also be seen in neurogenic

RESPONSE TO IS THERAPY COMMON ASSOCIATED CONDITIONS CELLULAR INFILTRATE Perimysial and perivascular inflammation; IFN-1 regulated proteins (MHC-1, MxA), MAC deposition on capillaries CD4+ dendritic cells; B cells; macrophages Yes Myocarditis, ILD, malignancy, vasculitis, other CTDs Endomysial and perivascular inflammation; ubiquitous expression of MHC-1 CD8+ T cells; macrophages; plasma cells Yes Myocarditis, ILD, other CTDs Necrotic muscle fibers; minimal inflammatory infiltrate; MHC-I and MAC deposition on sarcolemma of scattered nonnecrotic muscle fibers Macrophages in necrotic fibers undergoing phagocytosis Yes Malignancy, CTD, HMGCR antibody cases can be triggered by statin use Perimysial and perivascular inflammation; perimysial fragmentation with alkaline phosphatase staining; perimysial muscle damage with necrosis; MHC-I, HLA-DR, and MAC deposition on sarcolemma of perifascicular muscle fibers CD4+ dendritic cells; B cells; macrophages Yes Nonerosive arthritis, ILD, Raynaud's phenomenon, mechanic hands, and fever Endomysial and perivascular inflammation; ubiquitous expression of MHC-1 and HLA-DR; rimmed vacuoles; p62, LC3, TDP-43 aggregates; EM: 15–18 nm tubulofilaments; ragged red and COXnegative fibers CD8+ T cells; macrophages; plasma cells; myeloid dendritic cells; large granular lymphocytes None or minimal Granular lymphocytic leukemia/ lymphocytosis, sarcoidosis, sicca or Sjögren's syndrome disorders, however. Myositis-associated and myositis-specific antibod ies (MSAs) help to distinguish subtypes of IM, as discussed below. Electromyography (EMG) and nerve conductions studies (NCS) are useful in localizing the site of the lesion but are less specific in helping to determine the actual cause of a myopathy. EMG can be useful at times in guiding what muscle to biopsy, especially if muscles typically biopsied are normal on clinical examination. Imaging skeletal muscle can be helpful in assessing muscle involvement and revealing fatty replacement, atrophy, or edema within muscle or surrounding fascia. A muscle biopsy is often required to definitively distinguish one myopathy from another, if there is no characteristic dermatomyositis rash or myositis specific autoantibody. However, a muscle biopsy should be performed in every case of suspected PM to exclude IBM (if not clinically apparent) and other causes of myopathy. Diagnosis of IMNM is by definition based upon histologic findings but again is not needed if a patient has clinical features and anti-3-hydroxy-3-methylglutaryl-coenzyme reductase (HMGCR) or anti–signal recognition particle (SRP) antibodies. It is important to biopsy a muscle that is clinically affected but not too weak (e.g., Medical Research Council grade 4 out of 5 in strength); otherwise, one may just see end-stage muscle. A biopsy should always be coordinated with an experienced muscle histopathology laboratory. Patients with severe muscle pain, subjective weakness, and fatigue with normal strength and function on examination are not likely to have an IM. Polymyalgia rheumatica should be considered in older

individuals with an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) but normal CK and EMG. Fibromyalgia is likely in patients with a normal laboratory workup. In general, a muscle biopsy is not indicated unless there is objective weakness, an abnormal EMG, or elevated CK. SPECIFIC DISORDERS ■ ■DERMATOMYOSITIS Clinical Features DM manifests with symmetric, proximal greater than dis tal weakness along with a characteristic rash that includes the heliotrope rash (erythematous discoloration of eyelids with periorbital edema), Gottron sign (erythematous rash over the extensor surfaces of joints such as the knuck les, elbows, knees, and ankles), Gottron papules (raised erythematous rash over knuckles) (Fig. 377-1), V-sign (rash on the sun-exposed anterior neck and chest), shawl sign over the back of the neck and shoulders, nail bed telangiectasias, and subcutaneous calcium deposits. The weakness and rash usually accompany one another but can be separated by sev eral months. Furthermore, beyond "clas sic DM" with prominent muscle and skin manifestations, there is a spectrum of involvement such that some

patients have skin-predominant disease (only with a rash called amyopathic DM, or mini mal muscle disease called hypomyopathic DM), while others may present mainly with weakness and little or no visible skin changes. Patients may also have myalgias, arthralgias, dysphagia, and dysarthria. Cutaneous dis ease activity is highly relevant in DM; in comparison to other debilitat ing skin diseases including cutaneous lupus erythematosus, psoriasis, and atopic dermatitis, skin symptoms in DM patients are associated with an overall reduction in life quality. Pruritus can be especially debilitating. Dyspnea can occur from ventilatory muscle weakness or intrinsic lung involvement including interstitial lung disease (ILD), bronchopneumonia, and alveolitis. Pulmonary manifestations are often associated with anti-MDA-5 antibodies or with antisynthetase antibodies; myositis associated with the ASyS is now considered a dis tinct disorder (discussed below). DM can present in children (juvenile DM) or in adults. There is a higher risk for malignancy in adult-onset cases, ~15% within the first 2–3 years. A B FIGURE 377-1 Cutaneous manifestations of dermatomyositis. A. Macular erythema plaques (Gottron sign) and erythematous papules (Gottron papules) on extensor surface of fingers and B. elbow. C. Macular erythema plaques over anterior neck and chest (V-sign) and D. the posterior neck, shoulder, and upper back (Shawl sign). E. Nail bed changes with dilated capillaries. Laboratory Features Serum CK levels are elevated in 70–80% of patients; in 10% of those with normal CK, serum aldolase may be increased. Antinuclear antibodies can be positive but are a nonspecific finding. The myositis-specific antibodies (MSAs) that are specific for DM include anti–complex nucleosome remodeling histone deacetylase (anti-Mi-2), anti–transcription intermediary factor 1-γ (anti-TIF1-γ), anti–melanoma differentiation-associated gene 5 (anti-MDA5), anti– nuclear matrix protein 2 (anti-NXP-2), and anti–small ubiquitin-like modifier activating enzyme (anti-SAE). These antibodies are usually associated with characteristic clinical features, and recent studies sug gest that they are also directly involved in the pathogenesis of DM. Mi-2 antibodies are found in 15–20% of patients with DM and are typically associated with an acute onset, a florid rash, and prominent weakness but a good response to therapy and a favorable prognosis. Anti-MDA5 antibodies are found in 10–20% of DM patients and up to 65% of patients with clinically amyopathic DM. This antibody is associated with palmar rash, severe skin ulcerations from ischemia,

 C D E and rapidly progressive ILD. Anti-TIF1-γ, also known as p155, anti bodies are found in adult cancer-associated DM with an 89% specificity and 70% sensitivity. Thus, enhanced vigilance for underlying cancer is especially important in these patients. Anti-NXP-2 antibodies are found in as many as 17% of patients with DM and are also associated with calcinosis, subcutaneous edema, distal weakness, and dysphagia, as well as with cancer. Anti-SAE antibodies are present in 1.5–8% of DM and are associated with an underlying cancer in 14–57% of patients. Most manifest with a skin rash alone, and CK is often normal, but approximately one-third of patients have elevated aldolase levels. ILD can also be seen in anti-SAE DM, but unlike anti-MDA-5 amyo pathic DM, the ILD is usually mild. EMG of weak muscles shows increased insertional and spontaneous activity in the form of positive sharp waves and fibrillation potentials, or complex repetitive discharges along with early recruitment of smallamplitude, short-duration, polyphasic motor units. These findings are nonspecific and can also be seen in other myopathies. Skeletal muscle magnetic resonance imaging (MRI muscle) reveals edema in affected muscles and sometimes more specific findings of abnormalities of fascia suggesting fasciitis. Histopathology and Pathogenesis The characteristic histo pathologic abnormality on muscle biopsy is perifascicular atrophy (Fig. 377-2A); however, this finding is present in perhaps only 50% of patients. Immunohistochemical staining for myxovirus resistance protein A (MxA) is diagnostically

more sensitive and highly specific (Fig. 377-2B). The inflammatory cell infiltrate is predominantly peri vascular and located in the perimysium and is composed primarily of macrophages, B cells, and plasmacytoid dendritic cells. Recent studies have highlighted some variability in histologic abnormalities associated with different MSAs. Skin biopsies reveal cell-poor interface dermati tis, which is analogous to the perifascicular atrophy in that the basal

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders A B FIGURE 377-2 Perifascicular atrophy and myxovirus resistance protein A (MxA) expression in dermatomyositis. A. Perifascicular myofibers (black arrows) bordering on disrupted perimysial connective tissue are atrophic and basophilic on hematoxylin and eosin (H&E) stains. B. Perifascicular myofibers (white arrows) show intense staining for MxA protein along a gradient from superficial to deep; all capillaries show intense MxA expression (white arrowheads). layer of keratinocytes is most damaged; the inflammatory infiltrate is typically absent or minimal and, when present, is located mainly at the border zone of the dermis and epidermis. The pathogenesis of DM was traditionally attributed to an

antibody-mediated attack on endothelial cells, followed by complementmediated destruction of capillaries and watershed ischemia of muscle fibers. However, subsequent studies suggest that this is not likely the case. Immunoglobulin deposition is largely absent on endothelial cells, and complement deposition may be a secondary phenomenon. There is increasing evidence that the microvasculopathy and skin and muscle damage associated with DM are primarily due to toxicity from type I interferon (IFN)–mediated pathways, most likely IFN-β. As mentioned, there is increasing evidence that the MSAs are directly pathogenic. For example, anti-Mi-2 antibodies appear to be capable of entering myonuclei and inhibiting the CHD4/NuRD complex in the nucleosome. Prognosis In the absence of malignancy, prognosis is generally favorable in patients with DM, with 5-year survival rates ranging from 70 to 93%. Poor prognostic features are increased age, associated ILD, cardiac disease, and late or previous inadequate treatment. ■ ■POLYMYOSITIS Clinical Features PM is a heterogenous group of disorders that usually presents with symmetric and proximal weakness that worsens over several weeks to months. As with DM, there can be associated heart, lung, and joint involvement as well as an increased risk of cancer. Some epidemiologic studies suggest that the risk of cancer in PM is less than that in DM, but these older series likely included patients with IBM and dystrophies with inflammation who were misdiagnosed as having PM. Laboratory Features CK levels are always elevated in uncontrolled PM. A normal CK should alert clinicians to the possibility of IBM. EMG and skeletal muscle imaging can be abnormal, but the findings are not specific (Fig. 377-3). Histopathology and Pathogen esis Because PM is a heterogeneous category, muscle pathology varies sub stantially. Most often, patients with nonspecific inflammatory cells present in perimysial more often than endo mysial locations have been categorized as PM. A small minority of patients have a mononuclear inflammatory infiltrate that surrounds fibers with sarcolemmal expression of major histocompatibility complex (MHC-I) molecules (Fig. 377-4). FIGURE 377-3 Skeletal muscle magnetic resonance imaging (MRI) with short T1 inversion recovery (STIR) imaging in polymyositis. MRI of the thigh demonstrates bright signal indicative of edema/inflammation, particularly in the rectus femoris muscle. This contrasts with MRI in inclusion body myositis in which there is more selective involvement of the vastus lateralis and medialis with relative sparing of the rectus femoris (see Fig. 377-7F and G).

There is debate as to whether a true inva sion of myofibers occurs in PM or rather always indicates IBM. The inflamma tory infiltrate predominantly consists of CD8+ T cells and macrophages located in the endomysial, perimysial, and peri vascular regions. PM is heterogeneous, and its varied forms of pathogenesis are poorly understood. Prognosis Most patients with PM improve with immunotherapies but usually require lifelong treatment. Some retrospective studies suggest that PM does not respond as well as DM to these therapies. However, many of these older series of "PM" likely included patients who actually had IMNM, IBM, or other myopathies (including muscular dystro phies) that do not respond to immunotherapies. As in DM, poor prog nostic features are cancer, increased age, lung or cardiac involvement, and late or previously inadequate treatment. ■ ■OVERLAP SYNDROMES The term overlap syndrome is applied when an inflammatory myopa thy is associated with other well-defined connective tissue diseases (CTDs) such as scleroderma, mixed connective tissue disease (MCTD), Sjögren's syndrome, systemic lupus erythematosus (SLE), or rheuma toid arthritis. Overlap syndromes are usually responsive to immuno therapies. The exception is Sjogren's syndrome with coexisting IBM. ■ ■IMMUNE-MEDIATED NECROTIZING MYOPATHY Clinical Features IMNM, or autoimmune necrotizing myopathy, is characterized by the acute or insidious onset of symmetric, proximal more than distal weakness. Dysphagia, dysarthria, or myalgia may occur. Patients may have an underlying CTD (usually scleroderma or MCTD) or cancer (paraneoplastic necrotizing myopathy), or the condition may be idiopathic. There are at least two distinct forms of IMNM associated with specific autoantibodies (anti-HMGCR and anti-SRP). Anti-HMGCR myopathy can be seen in patients receiving statins, inhibitors of HMGCR, particularly in those aged >50 years. However, anti-HMGCR myopathy can develop in children and young adults without a history of statin use and can mimic a limb girdle mus cular dystrophy. Unlike the more common "toxic" myopathy associated with statin use, anti-HMGCR myopathy does not improve when statins are discontinued. Anti-SRP myopathies are notable for the presence of anti-SRP antibodies and a typically subacute, aggressive, and relatively refractory course.

FIGURE 377-4 Pathology of polymyositis. Muscle biopsy demonstrates endomysial infiltrates surrounding nonnecrotic muscle fibers. Laboratory Features CK levels are markedly elevated (usually

> 10 × normal) in IMNM and are associated with titers of anti-HMGCR or anti-SRP antibodies. EMG often shows increased insertional and spontaneous activity, including myotonic discharges. Skeletal muscle imaging findings are nonspecifically abnormal. Histopathology and Pathogenesis Muscle biopsies reveal multi focal necrotic and regenerating muscle fibers with a paucity of inflam matory cells (Fig. 377-5). However, some patients with anti-HMGCR myopathy have endomysial, macrophage-predominant infiltrates simi lar to what is seen in PM. Overexpression of MHC-I and membrane attack complex (MAC) molecules may be evident on sarcolemma of nonnecrotic fibers, and MAC deposition present on capillaries. The pathogenesis of IMNM is not completely understood and likely varies depending on subtype. A trial of a complement inhibitor in both antiHMGCR and anti-SRP myopathies failed to demonstrate any efficacy, so IMNM in these subtypes does not appear to be primarily comple ment driven. Interestingly, pathogenic biallelic variants in the HMGCR gene

> result in proximal weakness, myalgias, high CK, and dystrophic changes on skeletal muscle MRI and biopsies. Recent studies suggest that HMGCR antibodies may bind to the receptor on the sarcolemma and lead to accumulation of acetyl-CoA and subsequently an increase in lipids within muscle fibers. Recent studies also suggest that anti-SRP antibodies are directly causal to the associated IMNM. Prognosis Anti-HMGCR myopathy is often responsive to intra venous immunoglobulin (IVIG) monotherapy. However, anti-SRP FIGURE 377-5 Pathology of immune-mediated necrotizing myopathy. Muscle biopsy demonstrates scattered necrotic fibers with inflammatory infiltrate confined to those fibers undergoing myophagocytosis along with a few regenerating fibers.

myopathy and seronegative IMNM are generally much more difficult to treat, and aggressive immunotherapy is usually required. The pro gressive course despite immunotherapy and the marked weakness with atrophy can lead to a misdiagnosis of a limb girdle muscular dystro phy. There may be an increased incidence of cancer in patients with anti-HMGCR myopathy; thus, patients should undergo a malignancy workup.

CHAPTER 377 ■ ■ANTISYNTHETASE SYNDROME Clinical Features The presence of myositis, nonerosive arthritis, ILD, Raynaud’s phenomenon, mechanic hands, and fever associated with antibodies against aminoacyl-tRNA synthetase constitute the ASyS. Some patients have an erythematous rash, and muscle biopsies share histopathologic features of DM, which likely accounts for many of these patients being classified as having DM. Inflammatory Myopathies Laboratory Features Antibodies against aminoacyl-tRNA syn thetases are the most common MSA, present in 25–35% of patients with myositis. These include anti-Jo-1 (histidyl), anti-PL-7 (threo nyl), anti-PL-12 (alanyl), anti-EJ (glycyl), anti-OJ (isoleucyl), anti-KS (asparaginyl), anti-Ha (tyrosyl), anti-Zo (phenylalanyl), and other less common antibodies. The most common aminoacyl-tRNA syn thetase antibody is anti-Jo-1. CK is usually elevated in patients with ASyS and myositis. Those with ILD demonstrate reduced forced vital capacity and diffusion capacity on pulmonary function tests. Spiral chest computed tomography (CT) scans are best at demonstrating the honeycomb pattern of ILD. Skeletal muscle MRI and EMG show abnormalities similar to DM, PM, and IMNM. Histopathology and Pathogenesis Muscle biopsies demonstrate a predilection for perimysial damage including perimysial fragmenta tion and staining with alkaline phosphatase (Fig. 377-6), plasmacytoid dendritic cells and macrophages in the perimysium and around blood vessels, and MAC deposition on capillaries. Also similar to DM, there is perifascicular muscle fiber damage, but with ASyS, there is more perifascicular muscle fiber necrosis compared to DM, in which peri fascicular atrophy is more prominent. MHC-I, MHC-II (HLA-DR), and MAC deposits on muscle fibers may be seen on sarcolemma of perifascicular muscle fibers. The HLA-DR expression on muscle fibers suggests that ASyS is more driven by gamma-IFN than type 1 IFN. Recent studies suggest that the various antibodies may be directly pathogenic by binding to specific aminoacyl-tRNA synthetases thereby impairing protein synthesis. More work needs to be done to confirm these observations. Prognosis Most patients respond to treatment, although ASyS can be difficult to treat, in particular for patients with interstitial lung disease. Aggressive treatment, often with early rituximab, is war ranted in such cases. There does not appear to be an increased risk of malignancy. ■ ■INCLUSION BODY MYOSITIS Clinical Features IBM usually manifests in patients over the age of 50 years and is

slightly more common in men than women. It is associated with slowly progressive weakness and muscle atrophy that has a predilection for early involvement of the wrist and finger flexors in the arms and quadriceps in the legs (Fig. 377-7). Weakness is often asymmetric. Dysphagia is common and rarely can be the presenting feature. These clinical features can help distinguish IBM from PM and other forms of myopathy. The mean duration from onset of symptoms to use of wheelchair or scooter is ~15 years. There is no known increase in risk of malignancy. Laboratory Features CK levels can be normal or only slightly elevated (usually <10 times normal). Antibodies targeting cytosolic 5′-nucleotidase 1A (cN-1A) are detected in the blood in a third to more than two-thirds of IBM patients and are a highly specific diag nostic biomarker for IBM among patients with myopathy. Other blood biomarkers for IBM include the presence of an abnormal population of large granular lymphocytes on flow cytometry and a reduced CD4/CD8

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders A B C FIGURE 377-6 Pathology of myositis with anti-Jo-1 antibodies (antisynthetase syndrome). A. Perifascicular/perimysial muscle fiber atrophy and necrosis (thin arrow) associated with perimysial connective tissue is edematous and fragmented in appearance (thick arrow), hematoxylin and eosin stain. B. The perimysial connective tissue intensely stains red with alkaline phosphatase stain (arrowhead). C. Immunostaining demonstrates deposition of membrane attack complex (MAC) deposits on the sarcolemma of nonnecrotic perifascicular muscle fibers (open arrow). ratio with an increased CD8 count. Needle EMG may demonstrate large-amplitude, long-duration motor unit potentials that can be mis interpreted as neurogenic but reflect the chronicity of the myopathy. Muscle MRI may show a predilection for involvement of the flexor digitorum profundus in the arms and the vastus medialis and lateralis muscles with sparing of the rectus femoris muscle. Histopathology and Pathogenesis Muscle biopsies demon strate endomysial inflammatory infiltrates predominantly composed of highly differentiated CD8+ CD57+ T cells that express killer cell lectin-like receptor G1 (KLRG1) molecules, plus macrophages, that A B D E FIGURE 377-7 Muscle manifestations of inclusion body myositis (IBM; A–C). Finger flexor weakness can be (A) subtle and multifocal (black arrows), (B) moderate, or (C) severe. Note that even with complete paralysis of deep and superficial finger flexors, metacarpophalangeal joint flexion (arrows) is often maintained due to preservation of lumbricals. D. Ventral forearm atrophy (arrows). E. Atrophy of medial thighs due to loss of vastus medialis (arrows). F. Early IBM, with relatively preserved vastus medialis (arrows), in contrast to (G) advanced IBM with marked fibrous replacement of vastus medialis (arrows).

100.00 µm surround and invade nonnecrotic muscle fibers expressing MHC-I and MHC-II on the sarcolemma, along with fibers with rimmed vacuoles, cytochrome oxidase (COX)–negative fibers, and inclusions on light or electron microscopy (Fig. 377-8). The inclusions contain betasheet misfolded proteins (amyloid) but are difficult to appreciate with routine Congo red stain (they are seen on frozen but not paraffin sec tions). Immunostaining for p62 appears to be the most sensitive stain for detection of these inclusions. Importantly, rimmed vacuoles may not be seen in as many as 20–30% of muscle biopsies. In such cases, the presence of mitochondrial abnormalities (ragged red and COXnegative fibers) and immunostaining demonstrating p62 inclusions are C F G

A C FIGURE 377-8 Pathology of inclusion body myositis. A. Scattered muscle fibers with rimmed vacuoles and rare fibers with eosinophilic inclusions (arrow), hematoxylin and eosin stain. B. Cytochrome oxidase stain demonstrates an increased number of pale-staining or COX-negative

muscle fibers. C. Cytoplasmic inclusions stain positive with p62 within a muscle fiber (thick arrow). D. Electromicroscopy reveals 15- to 21-nm tubulofilamentous inclusions within a myonucleus. helpful in distinguishing IBM from PM (aside from the clinical pattern of muscle weakness). Immunostaining also demonstrates that TAR DNA-binding protein 43 (TDP-43), an intranuclear RNA/DNA-binding protein involved in the regulation of RNA processing, is extruded from the myonuclei in IBM. This is similar to what is found in neurons of patients with neurodegenerative disorders such as frontotemporal dementia (Chap. 443) and amyotrophic lateral sclerosis (Chap. 448). The pathogenesis of IBM is poorly understood. The prominent adaptive immune system abnormalities related to T-cell inflamma tion and the presence of a relatively specific autoantibody against a muscle protein indicate an autoimmune attack on muscle. The chronic and highly inflammatory environment within muscles in IBM may alter protein synthesis and degradation pathways in part via aber rant immunoproteasome expression. Additional histologic features, typically referred to as “degenerative,” include aggregation of various proteins including markers of endoplasmic reticulum (ER) stress and autophagy (e.g., p62 and LC3). Involvement of ER stress and autophagy has also been observed in other autoimmune diseases, such as primary biliary cholangitis (PBC), inflammatory bowel disease, and ankylosing spondylitis, some of which can be highly refractory to immunotherapy. As noted above, TDP-43, which is important for normal splicing of messenger RNA, is extruded from myonuclei in IBM; loss of TDP43–mediated splicing repression likely leads to abnormal inclusion of cryptic exons in skeletal muscle and aberrant translation of muscle proteins. Whether this tissue damage results directly from a pathogenic immune response or a secondary neurodegenerative process is unclear at this time. Prognosis The myopathy is slowly progressive and is not typically responsive to immunotherapies. Most patients require a scooter or wheelchair within 10–15 years of onset of symptoms. TREATMENT OF INFLAMMATORY MYOPATHIES (TABLE 377-2) DM, PM, ASyS, and IMNM are typically responsive to immuno therapy. High-dose glucocorticoids are considered the first-line treat ment. There is uncertainty regarding when to start second-line

 B D agents (e.g., methotrexate, azathioprine, mycophenolate, immuno globulin, or rituximab). The clinician must weigh with the patient the increased risks of immunosuppression versus possible benefits (e.g., faster improvement, steroid-sparing effects, and/or avoidance of morbidities associated with long-term glucocorticoid use). It is our general practice to start a second-line agent (typically methotrexate) with glucocorticoids in patients with severe weakness or other organ system involvement (e.g., myocarditis, ILD), those with increased risk of steroid complications (e.g., diabetics, osteoporosis, or postmenopausal women), and patients with IMNM who are known to have difficultto-treat myositis. When treatment is initiated with prednisone alone, a second-line agent is added in patients who fail to significantly improve after 2–4 months of treatment or in those who cannot be tapered to a low dose of prednisone. Many patients with IMNM do not respond to prednisone alone or even prednisone plus a second-line agent in combi nation. Many require triple therapy with prednisone, methotrexate, and IVIG and, if this fails, rituximab. In our experience and that of others, anti-HMGCR myopathy often responds to monotherapy with IVIG. Unfortunately, IBM does not typically respond to any known immu notherapy. The mainstay of treatment is physical and occupational therapy to improve function, and swallowing therapy (and sometimes esophageal dilation or cricopharyngeal myotomy) in those with dysphagia. ■ ■GENERAL GUIDELINES FOR USE OF

SPECIFIC IMMUNOTHERAPIES Glucocorticoids Treatment is initiated with prednisone (0.75–1.5 mg/kg up to 100 mg) administered as a daily morning single dose (the most common dose used in adults is 60 mg daily). In patients with severe weakness or comorbidities (e.g., ILD, myocarditis), treatment with a short course of intravenous methylprednisolone (1 g daily for 3 days) is recommended prior to starting oral glucocorticoids. Patients are generally maintained on high-dose prednisone until strength normal izes or until improvement in strength has reached a plateau (usually 3–6 months). Subsequently, prednisone can be tapered by 5 mg every 2–4 weeks. Once the dose is reduced to 20 mg every day or every other day,

TABLE 377-2 Immunotherapies for Inflammatory Myopathies THERAPY ROUTE DOSE SIDE EFFECTS MONITOR Prednisone Oral 0.75–1.5 mg/kg per day to start Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, cataracts, gastric irritation, osteoporosis, infection, aseptic femoral necrosis PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Methylprednisolone Intravenous 1 g in 100 mL/normal saline over 1–2 h, daily or every other day for 3–6 doses Azathioprine Oral 2–3 mg/kg per day; single a.m. dose Flu-like illness, hepatotoxicity, pancreatitis, leukopenia, macrocytosis, neoplasia, infection, teratogenicity Methotrexate Oral 7.5–20 mg weekly, single or divided doses; 1 day a week dosing Subcutaneously 20–50 mg weekly; 1 day a week dosing Same as oral Same as oral Cyclophosphamide Oral Intravenous 1.5–2 mg/kg per day; single a.m. dose 0.5–1.0 g/m2 per month × 6–12 months Cyclosporine Oral 4–6 mg/kg per day, split into two daily doses Tacrolimus Oral 0.1–0.2 mg/kg per day in two divided doses Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, teratogenicity Mycophenolate mofetil Oral Adults (1–1.5 g BID) Children (600 mg/m2 per dose BID) (no >1 g/d in patients with renal failure) Intravenous immunoglobulin Intravenous 2 g/kg over 2–5 days; then 1 g/kg every 4–8 weeks as needed Rituximab Intravenous A course is typically 750 mg/m2 (up to 1 g) and repeated in 2 weeks Courses are then repeated usually every 6–18 months Abbreviations: BUN, blood urea nitrogen; IVIG, intravenous immunoglobulin. Source: Reproduced with permission from AA Amato, JA Russell (eds): Neuromuscular Disorders. 2nd ed. New York: McGraw-Hill Education; 2016. the taper is slowed to 2.5 mg every 2–4 weeks. The goal is to taper pred nisone to ≤10 mg daily. Although most patients improve, the response may not be complete and many will require at least a small dose of pred nisone or a second-line agent to have a sustained remission. Serum CK levels are monitored; however, dose adjustments of prednisone and other immunotherapies are primarily based on the objective clinical examina tion and not the CK levels or the patients’ subjective response. When no response is noted after an adequate trial of high-dose prednisone, alter native diagnoses (e.g., IBM or an inflammatory muscular dystrophy) and a repeat muscle biopsy should be considered. Relapse of the myositis needs to be distinguished from steroid myopathy. Features suggesting a steroid myopathy include weakness developing while on high dosage, a normal serum CK, clinical features of steroid excess such as ecchymoses and “moon facies,” and absence of muscle membrane irritability on EMG. By contrast, patients experi encing relapses of myositis may become weaker during the prednisone taper, have increasing serum CK levels, and display abnormal sponta neous activity on EMG. Intravenous Immunoglobulin IVIG is most often used in patients refractory to prednisone and at least one second-line immuno suppressive agent. However, the ProDERM Trial Group found IVIG to be effective in a randomized, controlled trial in patients with DM, lead ing to U.S. Food and Drug Administration (FDA) approval. Thus, IVIG can be administered as first-line therapy in DM. In addition, IVIG is effective as a monotherapy in anti-HMGCR myopathy and may be the treatment of choice. A dose of 2 g/kg is divided over 2–5 days, and repeat infusions are given at monthly

intervals for at least 3 months. Subsequently, intervals can be lengthened or dosage decreased: 2 g/kg every 2 months or 1 g/kg per month.

Weight, blood pressure, serum glucose/potassium, cataract formation Arrhythmia, flushing, dysgeusia, anxiety, insomnia, fluid and weight gain, hyperglycemia, hypokalemia, infection Heart rate, blood pressure, serum glucose/potassium Blood count, liver enzymes Hepatotoxicity, pulmonary fibrosis, infection, neoplasia, infertility, leukopenia, alopecia, gastric irritation, stomatitis, teratogenicity Liver enzymes, blood count Bone marrow suppression, infertility, hemorrhagic cystitis, alopecia, infections, neoplasia, teratogenicity Blood count, urinalysis Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, teratogenicity Blood pressure, creatinine/ BUN, liver enzymes, cyclosporine levels Blood pressure, creatinine/ BUN, liver enzymes, tacrolimus levels Bone marrow suppression, hypertension, tremor, diarrhea, nausea, vomiting, headache, sinusitis, confusion, amblyopia, cough, teratogenicity, infection, neoplasia Blood count Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, aseptic meningitis, anaphylaxis, stroke Heart rate, blood pressure, creatinine/BUN Infusion reactions (as per IVIG), infection, progressive multifocal leukoencephalopathy Some check B-cell count prior to subsequent courses (but this may not be warranted) ■ ■SECOND-LINE THERAPIES Methotrexate Methotrexate is usually the second-line treatment of choice because most authorities believe it works faster than other agents. An oral dose of 5 or 7.5 mg/week is initiated and then gradually increased as needed up to 25 mg/week. If there is no improvement after 1 month of 25 mg/week of oral methotrexate, a switch to weekly par enteral (usually subcutaneous) methotrexate is the next step, with dose escalation by 5 mg weekly; only rarely is a dose >35 mg/week used. The major side effects of methotrexate are alopecia, stomatitis, ILD, terato genicity, oncogenicity, risk of infection, and pulmonary fibrosis, along with bone marrow, renal, and liver toxicity. Patients are concomitantly treated with folate or folinic acid. Azathioprine A recommended initial dose is 50 mg/d in adults, which can be increased by 50 mg every 2 weeks up to 2–3 mg/kg per day. Approximately 12% of patients develop a systemic reaction char acterized by fever, abdominal pain, nausea, vomiting, and anorexia that requires discontinuation of the drug. The major practical limitation of azathioprine is that 6–18 months of treatment are usually required before benefit can be seen. Patients can be prescreened for thiopurine methyltransferase (TPMT) deficiency that is associated with severe bone marrow toxicity from this drug. Mycophenolate Mofetil This drug inhibits the proliferation of T and B lymphocytes by blocking purine synthesis. It appears to be effec tive in different forms of myositis and is the second-line treatment of choice for myositis patients with ILD. The starting dose is 1.0 g twice daily and can be increased to 3 g daily in divided doses, if necessary. Mycophenolate is excreted through the kidneys; therefore, the dose should be decreased in patients with renal insufficiency. An advantage

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