15 Immunologic Disorders of Neuromuscular Junction and Muscle

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Introduction

A range of inherited and acquired processes can adversely affect the neuromuscular junction (NMJ) and muscle, many of which are not currently amenable to medical therapy, such as the muscular dystrophies. Autoimmune disorders of NMJ and muscle provide some of the limited number of peripheral neuromuscular diseases responsive to medical therapy and thus, are essential to recognize. Immune disorders account for the most common diseases of neuromuscular transmission and are very important to understand, not least because the autoimmune nature of disease provides opportunities for effective treatment. On the other hand, inflammatory disorders of muscle are a diverse group, some of which appear to have an immunologic basis, e.g., polymyositis and dermatomyositis, and possibly, inclusion body myositis.

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Neuromuscular Junction Anatomy

The neuromuscular junction is a synapse which transmits signals between a motor nerve terminal and a muscle fiber, the pre- and post-synaptic areas, respectively. The motor axon terminal contains active zones of arranged P/Q-type voltage-gated calcium channels (VGCC). Acetylcholine (ACh)-filled synaptic vesicles collect at these active zones. The primary synaptic cleft, which divides the pre- and post-synaptic areas, is comprised of a basal lamina that contains acetylcholinesterase, which catabolizes acetylcholine as it diffuses across the primary synaptic cleft. The post-synaptic membrane is comprised of junctional folds containing nicotinic-acetylcholine receptors (AChR) with ligand-gated cation channels. At the base of the folds are voltage-gated sodium channels (VGSC). The adult AChR is a tetramer containing two α subunits, and one each of β, δ, and ε subunits. Fetal AChR contain a γ subunit in place of the ε subunit. Each α subunit contains a ligand site for ACh as well as a main immunogenic region (MIR). ACh must bind to both ligand sites to activate the receptor channel [1].

When an action potential reaches the motor nerve terminal, VGCC are activated allowing influx of calcium into the nerve terminal. The influx of calcium triggers exocytosis of the ACh-synaptic vesicles and ACh is released into the primary synaptic cleft. ACh passively diffuses

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across the synaptic cleft to bind to post-synaptic AChR. Once activated, AChR undergo a conformational change allowing the influx of sodium and efflux of potassium, causing a small depolarization in the adjacent muscle membrane. A miniature endplate potential (MEPP) is the potential generated by the release of a single quantum of ACh. Since many synaptic vesicles are released, many MEPPs temporally and spatially summate to form an endplate potential (EPP). If this EPP is sufficient to depolarize the membrane to threshold, an action potential is generated and propagated by way of VGSC leading to muscle fiber contraction [1].

Myasthenia Gravis

Clinical Description

Myasthenia gravis (MG) was first described by Thomas Willis in 1672. It is characterized by fatigable weakness and prior to the discovery of anticholinesterase inhibitors and mechanical ventilation, it was a lethal disease. It is the most common disorder of neuromuscular transmission and the discovery of polyclonal autoantibodies directed against the post-synaptic neuromuscular junction in 1970 revolutionized the treatment and prognosis of MG. The most common presentation involves ocular, bulbar, and limb muscles. Fifty to sixty percent of patients present with ocular muscle weakness manifesting as ptosis and diplopia. An additional 30% will eventually develop ocular symptoms. Up to 90% of ocular myasthenic patients will eventually have generalized disease, causing bulbar, limb, and respiratory weakness [2]. Bulbar symptoms such as dysarthria and dysphagia can result in weight loss and aspiration pneumonia. Myasthenic crisis is the most severe manifestation when respiratory muscle weakness leads to respiratory failure.

Infants have a unique variety—neonatal myasthenia. Neonatal myasthenia occurs in progeny of myasthenic mothers within hours to days of birth. Arthrogryposis, generalized weakness, poor suck and swallow, and respiratory dysfunction can occur. Disease results from placentally transmitted AChR autoantibodies and can be fatal if there is antenatal involvement. If not, symptoms generally fully resolve in a few weeks and the infants are not at further risk for myasthenia gravis.

Diagnosis

The diagnosis is suggested by fatigable weakness of ocular, bulbar, or limb skeletal muscles. The clinical suspicion can be confirmed with autoantibody testing, short-acting anticholinesterase inhibitors such as edrophonium, and electrodiagnostic testing. Eighty percent of patients have antibodies against the acetylcholine receptor. These antibodies include binding, blocking, and modulating varieties, of which binding accounts for over 90% of acetylcholine receptor antibodies [1]. Seronegative myasthenia may be a manifestation of technical issues, antibodies with high affinity to their antigens, prolonged immunosuppression, or unknown autoantibodies. Cell-based assay for antibodies against clustered acetylcholine receptor antibodies is positive in nearly 40% of seronegative myasthenia gravis [3]. Up to a quarter of seronegative myasthenic patients have antibodies against muscle-specific kinase (MuSK) [1]. MuSK is a tyrosine kinase which regulates and maintains acetylcholine receptor clustering [4, 5]. These antibodies effectively disrupt clustering and function of the postsynaptic neuromuscular junction, without loss of acetylcholine receptors. Antibodies directed against other components of the neuromuscular junction have been discovered, including LRP-4, cortactin, and agrin, which account for a few percentage of patients though none are yet commercially available [6, 7]. Anti-striated muscle antibodies directed against thymic myoid cells are present in 27% of myasthenic patients and up to 90% of myasthenic patients with thymoma [8].

Edrophonium testing allows for transient improvement of symptoms in a clinically weak, easily tested muscle such as the deltoid or a ptotic eyelid. Such testing is 90–95% sensitive for generalized myasthenia and 80–90% sensitive and specific for ocular myasthenia. The Ice Cube test, in which an ice cube is placed on the muscle (this

only works with ptosis), can also be a useful bedside tool to diagnose myasthenia gravis [9]. Electrodiagnostic testing includes repetitive nerve stimulation and single-fiber electromyography (EMG). Repetitive nerve stimulation tests for compound motor action potential decrement from baseline and transient post-exercise facilitation. Single fiber EMG quantitatively assesses jitter, a manifestation of the variability in time it takes the EPP to reach threshold for action potential propagation at the neuromuscular junctions of individual muscle fibers. In myasthenia gravis, there is increased jitter with intermittent neuromuscular transmission blocking, clinically manifesting as weakness [1].

Pathophysiology

Myasthenia gravis results from an antibody-mediated, T-cell-dependent autoimmune attack on the postsynaptic neuromuscular junction with associated damage to, and simplification of, the postsynaptic membrane and reduction in number of AChR. The autoimmune nature of MG is thought related to loss of tolerance to self-antigens originating from thymic T cells. Up to 70% of myasthenics have thymic hyperplasia and another 15% have thymomas [1]. The hyperplastic thymus has an increased number of myoid cells which produce AChR similar to endplate AChR. These myoid cells are in close proximity to MHC-II interdigitating cells, which function as antigen-presenting cells, and are thought to present AChR fragments to autoreactive T cells. These T cells then aid AChR B cells in producing autoantibodies through the production of cytokines. AChR-specific T cells are also found in patients without MG, implying loss of tolerance or inhibitory control is necessary to lead to myasthenia gravis [10].

Antibodies in MG are heterogeneous with differing mechanisms, epitope recognition, and isotypes. This polyclonal expansion may explain the lack of correlation at times between symptoms and antibody titers. Most AChR antibodies bind to the α subunit, at the main immunogenic region (MIR). Antibodies may bind, block, or modulate the AChR. Binding antibodies crosslink two AChR, causing internalization and degradation, a process which is accelerated if more than one antibody binds. In this latter case, the clustered AChR are destroyed as well as VGSC, thereby increasing the depolarization threshold needed for generation of action potentials [10]. Unlike antibodies directed against AChR in myasthenia gravis, antibodies against MuSk are IgG4, which does not fix complement [5].

Complement plays a major role in the destruction of the postsynaptic membrane in AChR ab+ myasthenia gravis. Lytic phase activation and membrane attack complex (MAC) deposition at the NMJ causes shedding of postsynaptic junctional folds and AChR. The combination of antibody degradation of AChR and MAC destruction of junctional folds limits the surface area and the number of AChR available at the postsynaptic NMJ [10].

Treatment

Treatment can be symptomatic in purely ocular disease, using a longer acting form of acetylcholinesterase inhibitor such as pyridostigmine. Pyridostigmine is also efficacious in quickly but transiently treating fatigable weakness in generalized myasthenia. Pyridostigmine often has a paradoxic effect in MuSK+ myasthenia gravis, with no or adverse effect. Steroids are used as first-line immunomodulating therapy and can effectively induce clinical remission in up to 80% of patients, with sustained improvement beginning within 2 weeks. High-dose steroid induction can cause transient worsening of myasthenia and initiation requires inpatient hospitalization to monitor for respiratory failure. Second-line therapies include azathioprine, which inhibits T-cell proliferation, and mycophenolate mofetil, which inhibits an enzyme crucial in purine synthesis and critical for B- and T-cell production. Cyclosporine was proven effective by a prospective, double-blind, placebo-controlled trial but is usually limited to patients who fail steroids and azathioprine, due to kidney and liver toxicity, and hypertension. A

double-blind, controlled, randomized trial of methotrexate in myasthenia gravis failed to show improvement in the primary endpoint, decrease in prednisone dose, though did show trends toward improvement in several secondary measures [11]. A Cochrane review of immunosuppressants in MG found improvement with cyclophosphamide or with cyclosporine with or without corticosteroids in small randomized control trials. Other small randomized control trials showed no improvement with azathioprine, mycophenolate mofetil, or tacrolimus [12].

Intravenous immunoglobulin (IVIG) causes transient improvement in 70% of myasthenic patients within 5 days, and can last for 8–12 weeks. A Cochrane review showed benefit of IVIg over placebo, but no difference between IVIG and plasma exchange [13]. There was no difference between 1 and 2 g/kg of IVIG or between IVIG and oral methylprednisolone. Plasma exchange rapidly but temporarily reduces antibody titers and is a very important part of the treatment of myasthenic crisis [13]. It can also be useful in patients refractory to other treatments or in those needing immediate but transient improvement, such as prior to thymectomy. Thymectomy provides long-term benefit which may be delayed for 6–12 months and is usually done in patients between 18 and 55 with generalized disease. It is essential in the 15% of myasthenic patients with thymomas. The goal of thymectomy is improved symptoms, decreased medication requirement, and an increased rate of remission post thymectomy. What was missing to prove the value of thymectomy was a randomized trial. This was finally accomplished and conclusively showed not only improvement in the Quantitative Myasthenia Gravis score but also significant reduction in prednisone dose [14]. Rituximab, an anti-CD20+ monoclonal antibody, may be efficacious, particularly in MuSK ab+ myasthenia [15]. Eculizamab, an inhibitor of the C5 component of the complement cascade, therefore inhibiting the MAC, was approved in Europe and the USA for use in refractory seropositive generalized myasthenia gravis in late 2017 based on the results of the REGAIN trial [16].

Lambert Eaton Myasthenic Syndrome

Clinical Description

Lambert-Eaton myasthenic syndrome (LEMS) was initially described in 1953, as potentially the first paraneoplastic disease. LEMS presents insidiously with symmetric weakness and fatigue in a proximal to distal gradient. Muscle aches and paresthesias are often present. Reflexes are characteristically absent, but return transiently following voluntary muscle contraction [17]. Seventy-five percent of patients with LEMS have dysautonomia manifesting as dry mouth, dry eyes, impotence, constipation, difficulty with micturation, decreased sweating, and pupillary abnormalities [17]. Unlike myasthenia gravis, oculomotor abnormalities and respiratory crises are uncommon.

While 50% of LEMS patients are associated with paraneoplastic syndrome, three-quarters of the neoplasms are not diagnosed until 1–5 years following neurological presentation. Paraneoplastic LEMS is often associated with other paraneoplastic syndromes such as cerebellar degeneration, sensorimotor polyneuropathy, and encephalomyelitis, which helps to distinguish this from the autoantibody variety [17, 18].

One striking clinical feature pathognomonic to disorders of presynaptic neuromuscular junction transmission is facilitation. Muscles and reflexes that were weak return to nearly normal strength, transiently, after exercise.

Diagnosis

Diagnosis is based on a high degree of clinical suspicion. Electrodiagnostic findings of reduced compound muscle action potentials (CMAP) with greater than 100% increment of CMAP amplitude following 10–30 s of exercise (post-exercise facilitation) are diagnostic of a pre-synaptic disorder. Similar post-exercise facilitation is seen following 20–50 Hz repetitive nerve stimulation, which is not recommended in the conscious patient due to its great discomfort. Slow repetitive nerve stimulation (2–5 Hz)

reveals >10% decrement pre-exercise with repair of decrement and increase in CMAP amplitude immediately following exercise and subsequent decrement after 2–3 min. Singe-fiber EMG shows abnormal jitter with blocking, but jitter decreasing with an increase in firing rate. Electrodiagnostic testing cannot differentiate paraneoplastic from autoimmune LEMS [17].

Antibodies against P/Q-type voltage-gated calcium channels (VGCC) are found in up to 85% of LEMS patients. High-titers strongly support the diagnosis, whereas low titers can be seen in non-LEMS patients and absent titers do not rule out the diagnosis. Anti-Hu or other antinuclear neuronal antibodies are suggestive of paraneoplastic LEMS in association with small cell lung carcinoma [18].

Once the diagnosis is made, the search for neoplasm should focus on small cell lung carcinoma, the primary neoplasm implicated in paraneoplastic LEMS. Other neoplasms associated include T-cell leukemia, lymphoma, Castleman's syndrome, and reticulum-cell sarcoma [19].

Pathophysiology

LEMS is caused by a polyclonal antibody attack directed against the P/Q VGCC located on the pre-synaptic membrane of the neuromuscular junction. VGCCs contain α1, β, and α2/δ subunits, with the α1 subunit serving as the ligand-binding site as well as containing the calcium conductance channel. The autoimmune attack results in loss of calcium channels and disorganization of the active zones, where exocytosis of acetylcholine-containing synaptic vesicles occurs. There is reduction in acetylcholine release into the NMJ, resulting in fewer MEPPs at the post-synaptic terminal, resulting in a decreased EPP. If the EPP is below threshold for action potential generation, then neuromuscular transmission is unsuccessful and weakness occurs. Exercise serves to increase ingress of calcium, allowing for increased synaptic vesicle release, increased numbers of MEPPs and an EPP sufficient to reach threshold, thus explaining facilitation [17].

Treatment

In paraneoplastic LEMS, treatment is directed at the primary neoplasm, removal of which often reduces symptoms or allows remission [17]. Symptomatic treatments include pyridostigmine, and 3,4-diaminopyridine (3,4 DAP). Pyridostigmine, an acetylcholinesterase inhibitor, inhibits the breakdown of acetylcholine, effectively enhancing the MEPP amplitudes allowing for increased EPP and successful neuromuscular transmission. Diaminopyridine inhibits voltage-gated potassium channels, which lengthens the action potential and prolongs calcium entry into the presynaptic terminal, thereby increasing acetylcholine release into the primary synaptic cleft. It has been the subject of two recent randomized, controlled trials, one testing the base version of DAP (DAPPER) and the other a more stable, salt form (Catalyst sponsored trial). Both showed significant efficacy [20, 21]. FDA approval is pending for both and the two forms have precipitated a discussion about pharmaceutical company pricing and unexpected consequences of the Orphan Drug program of the FDA [22].

Immunologic therapy is an important mainstay in patients not undergoing cancer treatment. Prednisone and azathioprine or their combination has been shown to be efficacious. Plasma exchange and IVIG are used as in myasthenia to remove autoantibodies or suppress their production. A Cochrane review of treatments in LEMS showed improvement in strength in two studies of 3,4-DAP with 38 total patients and one study of 9 patients using IVIg. Other LEMS treatments have not been studied in randomized, controlled trials [23].

Polymyositis

Clinical Description

Polymyositis (PM) presents insidiously in adults with progressive symmetric proximal weakness. Symptoms include difficulty climbing stairs, getting out of a chair, and combing hair. Up to 50% have myalgias and tenderness to palpation.

Atrophy occurs in severe weakness with associated reduced reflexes. Pharyngeal and neck extensor weakness may lead to dysphagia and head drop. In advanced cases, there may be involvement of respiratory muscles and distal hand muscles. Facial and extraocular muscles are typically spared. Other organ system involvement includes cardiac disease due to myocarditis and interstitial lung disease (ILD). Interstitial lung disease can be a result of methotrexate toxicity or in 10% of PM, seen in association with anti-Jo or ribonucleoprotein antibodies [24].

Diagnosis

The diagnosis of PM is based on clinical suspicion, muscle enzyme testing, EMG, and muscle biopsy. Characteristically, creatine kinase can be up to 50 times the upper limit of normal. Evaluating for myositis-associated antibodies (MAA) or myositis-specific antibodies (MSA) is important for staging the disease and stratifying risk [24]. EMG findings include short-duration, low-amplitude polyphasic potentials with abnormal spontaneous activity which is characteristic of necrotic myopathies such as PM [24]. Muscle biopsy is the most specific diagnostic test, revealing endomysial inflammation with muscle fiber necrosis (Fig. 15.1). CD8+ T cells invading non-necrotic muscle fibers expressing MHC-1 antigens are characteristic [25]. Imaging is playing an increasing role in diagnosis (see section "Diagnosis" of DM below).

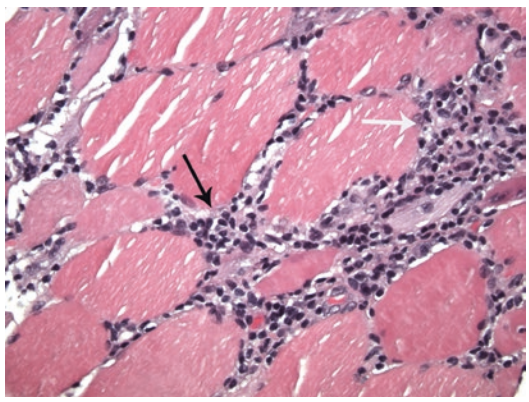

Fig. 15.1 Polymyositis. Muscle fibers are surrounded by inflammatory cells, mainly lymphocytes (black arrow). At least one fiber in this figure is undergoing myophagocytosis (white arrow). H&E stain, ×400

Pathophysiology

PM is thought due to a T-cell-mediated attack on muscle fibers. Macrophages and cytotoxic CD8+ T cells surround and eventually invade non-necrotic muscle tissue, eventually leading to muscle fiber destruction. These cytotoxic T cells recognize an unknown antigenic target in association with MHC-1 antigens expressed by muscle fibers. T cells induce muscle fiber necrosis via perforin, a membrane lytic molecule [25, 26].

In up to 20% of inflammatory myopathies, there are autoantibodies against nuclear and cytoplasmic antigens (Table 15.1). Ribonucleoproteins are involved in translation and protein synthesis and are the target of several anti-cytoplasmic antibodies such as Jo-1 (the most common). These autoantibodies are not specific to PM as they can be seen in both dermatomyositis (DM) and inclusion body myositis (IBM), and occur in ILD in the absence of myositis [27, 28].

Anti-synthetase syndrome is the most common syndrome with myositis and autoantibodies. The typical presentation is ILD and myositis, often with Raynaud's, fever, arthralgia, and thickened cracked fingers known as "mechanic's hands," often with a more acute, crescendo presentation. Anti-Jo-1, directed against histidyl-transfer RNA synthetase, comprises up to 75% of the anti-synthetase antibodies and accounts for 60–80% of MSA patients, with PL-7, PL-12, EJ, OJ, or KS found in the remainder. There is a threefold increase in mortality compared to PM, perhaps due to its association with ILD [27].

Overlap syndromes exist between connective tissue diseases and either PM or DM. Systemic lupus erythematosus has an associated myositis in 8% of patients. Of these patients, anti-nuclear antibodies directed against native DNA and anti-Sm are specific to SLE-myositis patients. Other antibodies include anti-SSA (Ro), anti-SS-B (La), and anti-U1 ribonuclear protein, but are not specific to SLE-myositis patients. Myositis is rarely associated with Sjogren's syndrome with antibodies against the ribonucleoproteins SS-A

Table 15.1 Antibodies seen in inflammatory myopathies

Autoantibody	Antigen target	Clinical presentation
Anti-Jo 1	Histidyl t-RNA synthetase	Antisynthetase syndrome
Anti-PL-7	Threonyl-t-RNA synthetase	Polyarthritis
Anti-PL-12	Alanyl-t-RNA synthetase	
Anti-EJ	Glycyl-t-RNA synthetase	ILD
Anti-KS	Asparaginyl-t-RNA synthetase	"Mechanic" hands
Anti-OJ	Isoleucyl-t-RNA synthetase	Myositis
Anti-SRP	325-kDa ribonucleoprotein	Anti-SRP syndrome (muscle, cardiac involvement, steroid resistant)
Anti-Mi2	Transcription peptide complex	DM ± ILD
Anti-Scl-PM	Peptide complex	Scleroderma, myositis, scleroderma/PM or DM
Anti-Ku	Heterodimer associated with DNA-dependent protein kinase	Scleroderma/PM or DM overlap syndromes, SLE, scleroderma, MCTD, Sjogren's, thyroiditis, pulmonary hypertension
Anti-PMS	DNA binding protein complex	PM and DM
Anti-56 kDa	Ribonucleoprotein	PM and DM of childhood onset

ILD inflammatory lung disease, *SRP* signal recognition protein, *DM* dermatomyositis, *PM* polymyositis, *SLE* systemic lupus erythematosus, *MCTD* mixed connective tissue disease

and SS-B. Up to 13% of rheumatoid arthritis is associated with myositis. Scleroderma has myositis as a feature in 5–17%. In North America, 25% of patients with scleroderma and myositis have anti-PM-Scl (anti-PM1) antibodies, while in Japan, anti-Ku antibodies are more common. Anti-U1 ribonuclear protein is seen in mixed connective tissue disease [24]. Anti-signal recognition particle antibodies were previously associated with PM, but recent studies have shown they are part of a distinctive syndrome consisting of a steroid-resistant necrotizing myopathy with little inflammation, and MAC deposition and capillary loss [29, 30] (see below).

PM can be seen during the course of other autoimmune diseases such as Crohn's disease, vasculitis, sarcoidosis, celiac disease, primary biliary cirrhosis, Behcet's disease, and Hashimoto's disease, among others. Giant cell myositis is associated with thymomas and as such can also be seen in patients with myasthenia gravis.

Treatment

Corticosteroids remain the mainstay of treatment for PM with more than 80% of patients responding to some degree. Noticeable clinical improvement occurs within 3–6 months. For patients who do not respond, or who relapse during prednisone therapy, second-line agents include azathioprine, methotrexate, cyclophosphamide, rituximab, cyclosporine, mycophenolate mofetil, IVIG, and plasmapheresis. Methotrexate is a folate antagonist used in patients who respond poorly to steroids or azathioprine [24]. IVIG has been shown to provide significant improvement in muscle strength over 3 months [31]. Rituximab may be beneficial in refractory PM [32], particularly in patients with MSAs [24]. Relapses should be differentiated from steroid myopathy, which has normal CK levels, no abnormal spontaneous activity on needle EMG and type 2 fiber atrophy on muscle biopsy. The myositis, arthralgias, and systemic symptoms of anti-synthetase syndrome tend to respond to steroids, while the ILD can be steroid responsive, depending on subset. Undetectable anti-synthetase antibodies after treatment predict a favorable prognosis [27]. A Cochrane review of treatments for both PM and DM found equal efficacy with azathioprine, cyclosporine, and methotrexate, with the latter having a more favorable side effect profile [31].

Dermatomyositis

Clinical Description

Dermatomyositis (DM) occurs in children and adults and is characterized by skin changes which accompany or may precede weakness.

An edematous bluish-purple discoloration of the upper eyelid, "heliotrope rash", flat erythematous rash of the face, chest and extensor surface dermatitis exacerbated by sun exposure, and Gottron's rash, a erythematous, scaly, violaceous rash on the knuckles, are all characteristic. Nail changes with dilated capillary loops, thickened cuticles, and rough, cracked "mechanic hands" may occur. Subcutaneous calcifications occur more frequently in children and may cause ulcerations [24]. Weakness occurs subacutely with a proximal to distal gradient.

Cardiac manifestations include cardiomyopathy, conduction defects, and tachyarrhythmia similar to polymyositis. Pulmonary symptoms are related to interstitial lung disease, methotrexate toxicity, or thoracic muscle weakness. Gastrointestinal ulceration, joint contractures, and systemic symptoms occur. Rarely, renal failure and rhabdomyolysis may be seen in acute presentations. DM has an increased risk of malignancy which can precede the diagnosis, but usually occurs within 2 years of the myositis. Women over the age of 40 years appear to be at greatest risk of associated neoplasm. Commonly associated cancers include breast, lung, ovarian, and gastrointestinal [24]. Amyopathic dermatomyositis, i.e., dermatomyositis without muscle involvement, occurs in about 20% of patients [24].

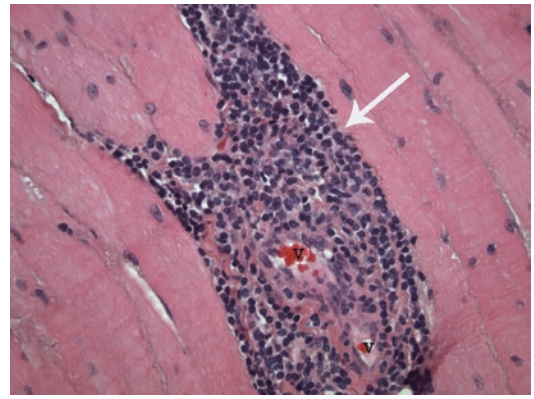

Fig. 15.2 Dermatomyositis. Inflammatory cells, mainly lymphocytes (arrow) are seen completely surrounding and invading two small, interstitial blood vessels (V). H&E stain, ×400

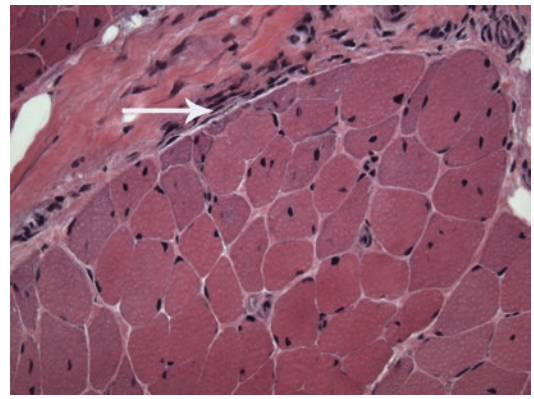

Fig. 15.3 Dermatomyositis. Unlike polymyositis, dermatomyositis is a vasculitis, which leads to ischemic damage along the periphery of the muscle fascicles, resulting in "perifascicular atrophy" (arrow). H&E stain, ×400

Diagnosis

Skin manifestations of dermatomyositis are pathognomonic. Clinical diagnosis can be confirmed with muscle enzyme testing, electrodiagnostic testing, and muscle biopsy. Creatine kinase often reflects disease severity and can be increased up to 50-fold. Testing for MAA/MSAs is important for staging the disease and stratifying risk [24]. Electromyography reveals myopathic features interspersed with rare neurogenic motor unit potentials and abnormal spontaneous activity. Perifasicular inflammation, endothelial hyperplasia, and capillary loss are characteristic muscle biopsy features (Figs. 15.2 and 15.3). Frequently, a high percentage of B cells and an increased CD4+/CD8+ ratio may be found on immunohistochemistry of muscle [24]. Perifasicular atrophy (Fig. 15.3) results from watershed zone microinfarcts within muscle fascicules and is highly suggestive of DM. Magnetic resonance imaging is being used more often in both PM and DM, to detect affected muscles for biopsy, and to determine active inflammation (T2-weighted images) or atrophy (T1-weighted). Ultrasonography can distinguish between normal and pathologic muscle and is easier and less expensive than MRI, particularly for determining muscles best suited for biopsy [24].

Pathophysiology

Dermatomyositis is most commonly thought to be caused by antibody-mediated damage of muscle capillaries with subsequent necrosis, capillary loss, and focal muscle ischemia. While the antigen is unknown, it is thought to be a component of the endothelium of endomysial vessels. Activation of complement C3 leads to the formation and deposition of C3bNEO and MAC deposition on endomysial capillaries. MAC deposition leads to endothelial damage and subsequent capillary necrosis [24]. The remaining capillaries dilate to compensate for the capillary loss, and perifasicular atrophy occurs as a result of hypoperfusion to this watershed area. Micro-infarcts occur as a result of necrosis of larger intramuscular vessels. Muscle fiber damage also occurs from the recruitment of macrophages and T cells by chemotactic factors as a result of complement activation.

Treatment

The mainstay of treatment is corticosteroids in high doses. The mechanism of action is unclear but may involve inhibiting movement of lymphocytes to areas of muscle inflammation. Steroid-sparing medications include azathioprine, methotrexate, cyclosporine, and for refractory disease, IVIg and rituximab should be considered. A recent randomized trial in juvenile dermatomyositis compared prednisone to prednisone and methotrexate and to prednisone and cyclosporine. Both combinations were significantly more efficacious than prednisone alone, and the combination of prednisone and methotrexate had fewer side effects than with cyclosporine [33]. A Cochrane review of treatments showed benefit in DM with IVIg versus placebo in one small trial [31]. Rituximab given early or late was studied in a randomized, double-blind trial of refractory PM and DM. Steroids and other immunosuppressives were allowed at entry. There was no difference between the two rituximab regimens, and 83% of patients with refractory disease met the definition of improvement [32].

Inclusion Body Myositis

Clinical Description

Inclusion body myositis (IBM) is the most common primary muscle disorder in people older than 50 years. There is a male predominance and IBM is usually sporadic with rare autosomal recessive inheritance. The course is one of indolent progression of asymmetric weakness affecting the legs before the arms. Patients often present with falling and tripping from quadriceps and foot plantar flexor weakness. Finger flexor weakness contributes to difficulty with fine motor skills such as buttoning and opening jars. The combination of quadriceps and finger flexor weakness and atrophy is characteristic of IBM. Weak quadriceps muscles contribute to depressed patellar reflex. Other muscles commonly affected include biceps, triceps, iliopsoas, and tibialis anterior. Weakness is often asymmetric. Dysphagia is a presenting feature in 30–40%. Facial weakness can occur along with other cranial nerves but respiratory muscles are relatively spared [29, 34].

Diagnosis

Diagnosis is based on clinical, laboratory, electrodiagnostic, and biopsy findings. Creatine kinase is often elevated two- to threefold but can be up tenfold or may be normal. Anti-cytosolic 5′-nucleosidase 1A (cN1A) autoantibodies have been reported to be specific for the diagnosis of IBM, though have also been reported in other autoimmune diseases [29]. Electrodiagnostic testing helps to exclude neurogenic conditions such as amyotrophic lateral sclerosis. Myopathic features are most commonly seen on needle electromyography though in 1/3 of patients neurogenic features may be interspersed with myopathic motor unit potentials. Spontaneous activity is seen due to myonecrosis but may be underwhelming. Muscle biopsy (Fig. 15.4) is the standard for diagnosis. Findings include rimmed vacuoles, endomysial inflammation, eosinophilic

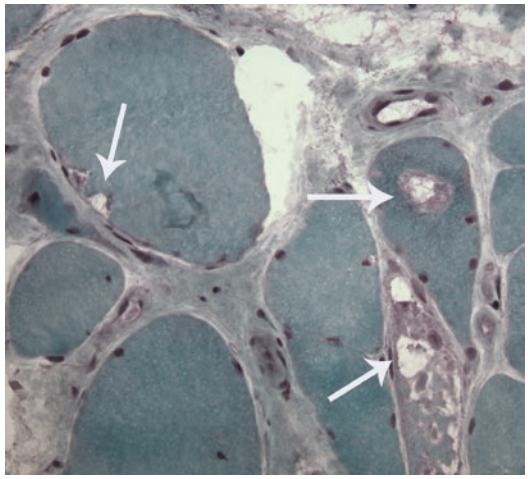

Fig. 15.4 Inclusion body myositis. Rimmed vacuoles (arrows) within muscle fibers are a prominent part of the pathology of inclusion body myositis. Modified Gomori trichrome stain, ×400

inclusions, swollen or vacuolated nuclei, and a combination of hypertrophic and atrophic fibers. Red ragged fibers may be seen due to abnormal mitochondria after nuclear damage. CD8+ T cells invading non-necrotic muscles fibers provide evidence for definite IBM. Electron microscopy reveals intranuclear and intracytoplasmic filamentous inclusions, approximately 10–18 nm in diameter.

Pathophysiology

Muscle biopsy findings in IBM include significant endomysial inflammation similar to PM. Auto-aggressive CD8+ T cells comprise 70% of the endomysial inflammatory cells and preferentially invade non-necrotic muscle, implicating inflammatory cells in muscle fiber necrosis. MHC-1 antigens have also been found surrounding these inflammatory cells, and the presence of cN1A antibodies implicates an autoimmune process [29]. Other pathologic features (rimmed vacuoles, abnormal protein aggregates, and the lack of response to immune therapies) suggest a degenerative process [29].

Treatment

Treatment in IBM is largely supportive, as no effective pharmacologic treatment has been found [35]. Steroids, azathioprine, cyclophosphamide, methotrexate, beta interferon 1a, lymphoid irradiation, and IVIG have shown no benefit. Cricopharyngeal botulinum toxin may be beneficial in patients with severe dysphagia [36].

Immune-Mediated Necrotizing Myopathy

Immune-mediated necrotizing myopathies are characterized by subacute weakness of limb muscles, elevated creatine kinase, myopathic EMG, and pathologic findings on muscle biopsy, including muscle fiber necrosis and very limited, if any, inflammatory infiltrates [29]. The autoimmune nature is bolstered by more recent delineation of an association with at least two particular myositis-specific antibodies, directed either at the signal recognition particle (SRP) or at 3-hydroxy-3-methylglutarylcoenzyme A reductase (HMGCR). The relative absence of inflammation and the presence of MSAs help differentiate these patients from those with other inflammatory myopathies (Fig. 15.5a). Patients can respond to immunosuppressive therapy, though usually requiring steroids and one or more additional immunotherapeutic agents (such as IVIG, MTX, AZA, rituximab) [29].

$CD68^+$ $iNOS^+$ macrophages and a Th-1 immune environment are involved in ongoing phagocytosis of necrotic muscles fibers and activation of the classical complement cascade occurs [30]. IgG1 isotype is seen amongst both anti-SRP and anti-HMGCR antibodies, which activates complement. C5b9 (Fig. 15.5b) and C1q, and both autoantibodies are deposited on the sarcolemmal membrane, indicating a direct role of the antibodies and that complement activation plays a pathogenic role [29, 30]. CK levels have been found to correlate with both the proportion of necrotic fibers as well as the titer of anti-SRP antibodies [30].

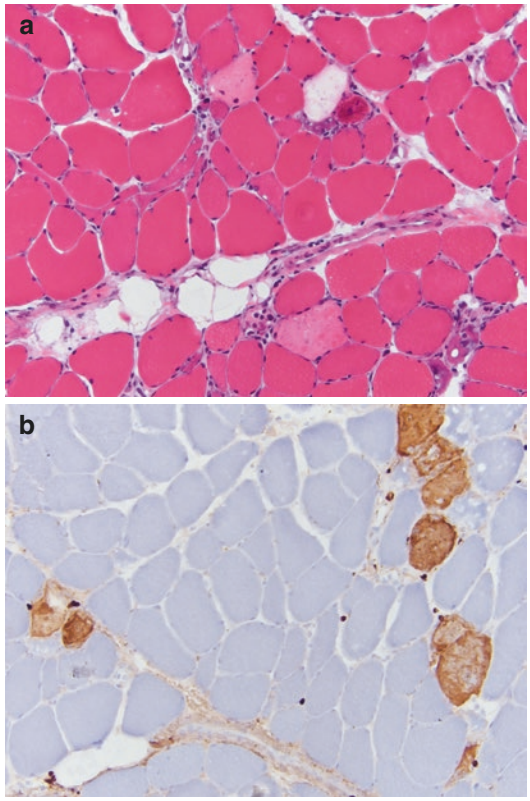

Fig. 15.5 Immune-mediated necrotizing myopathy due to anti-SRP antibodies. (**a**) Myonecrosis affecting muscle fibers in the absence of significant inflammatory response. H&E, ×20. (**b**) Multiple muscle fibers showing reactivity to C5b9, ×20

Drug-Induced Inflammatory Myopathies

Immune checkpoint inhibitor (CI) therapy unleashes the body's immune system to attack cancer and has become an increasingly useful therapeutic strategy in more severe stages of cancer, with remarkable success. However, in allowing this avenue of attack on cancer, it opens the door to autoimmune attack upon other, healthy tissues such as neuromuscular junction and skeletal muscle. CI-induced disease is similar to non-CI disease in therapy but can differ in pathophysiology [37].

There are three targets of checkpoint inhibition with several target-specific monoclonal antibodies approved for use. Targets include cytoplasmic t-lymphocyte-associated antigen-4, targeted by ipilimumab; programmed cell death-1, targeted by pembrolizumab and by nivolumab; and programmed cell death ligand-1, targeted by avelumab, ateozolizimab, and durvalumab [37]. Neurologic adverse events are rare, in the 1–3% range, with neuromuscular involvement accounting for a small portion of that. Myasthenia gravis, either as exacerbation of known disease or as de novo disease, is the most frequent neuromuscular adverse event. Patients can be AChR antibody positive or negative, but have not been MuSK antibody positive. Onset is usually within 3 months of onset of therapy, often within the first 6 weeks. Rhabdomyolysis, myositis, and myocarditis may also occur. Treatment requires high dose steroids and often, IVIG or plasmapheresis [37].

Myositis is less frequent, especially when encountered as the sole manifestation of autoimmunity. It can respond to steroids or steroid-sparing immunosuppressants [37].

Other Myopathies

Eosinophilic myositis is a rare form of PM in which there is peripheral eosinophilia and eosinophilic infiltrates of the endomysium. The cytokine IL-5 is thought to activate eosinophils which invade muscle fibers (Fig. 15.6), degranulate and release cytotoxic materials. Eosinophilic myositis has occurred as a consequence of calpain-3 mutations, which often causes adult-onset limb girdle muscular dystrophy (LGMD type 2A), in children under 10 years with elevated creatinine kinase and peripheral eosinophilia [38, 39].

Several muscular dystrophies are associated with inflammation found on histochemical study of muscle. Laminin α2 (merosin) deficiency can have an associated perimysial, endomysial, and perivascular B- and T-cell infiltration with myofiber necrosis [40]. Macrophages and lymphocytes

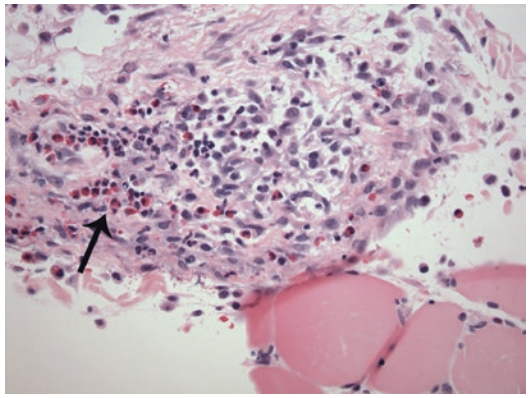

Fig. 15.6 Eosinophilic myositis. A cluster of inflammatory cells with a prominent eosinophilic component (arrow) can be seen adjacent to a group of muscle fibers. The patient was thought to have Churg-Strauss syndrome. H&E stain, ×400

with MHC-I expression have been found in LGMD2L, Duchenne muscular dystrophy, and Becker muscular dystrophy, and inflammation has been found in up to 40% of dysferlinopathy (LGMD2B) biopsies [41]. Inflammatory cells are found in 40–80% of biopsies in facioscapulohumeral muscular dystrophy (FSHD) [42]. A compelling hypothesis is that sarcolemmal disruption due to genetically induced defects results in repeated cycles of muscle fiber degeneration and regeneration, thus triggering chronic inflammatory responses leading to functional muscle tissue being replaced by non-functional fibrotic tissue, perpetuating and exacerbating the underlying muscle disease. The benefit of steroids in Duchenne muscular dystrophy may arise from its anti-inflammatory effects. Chronic inflammation may result from calcium overflow-induced inflammation, reactive oxygen species, and/or activation of the NF-κB inflammatory pathway. There are several potential therapeutic targets which are under investigation [43].

While sarcoidosis may have a variety of neurologic presentations, 50–80% of patients with systemic sarcoid have muscle granulomas, over 90% of which are asymptomatic. Symptomatic sarcoid myositis presents with proximal weakness, myalgias, muscle tenderness, and weight loss. Chronic sarcoid myopathy presents as proximal muscle wasting of limb, trunk, and neck

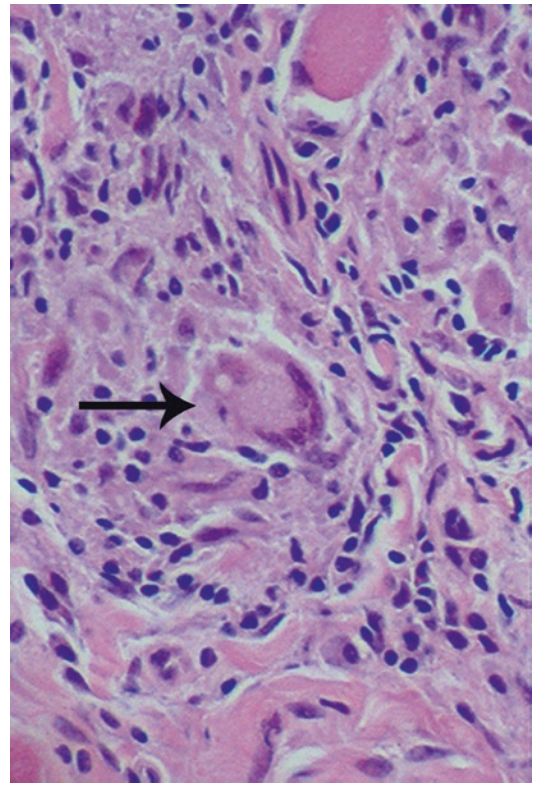

Fig. 15.7 Sarcoid myopathy. A multinucleated giant cell (arrow) is seen within a non-caseating granuloma. H&E stain, ×400

muscles. Non-caseating granulomas form in the muscle (Fig. 15.7) as a result of accumulation and aggregation of CD4+ helper T cells. The mainstay of treatment for systemic and symptomatic myopathic sarcoid is corticosteroids, though chronic sarcoid myopathy often responds poorly. Immunosuppressants such as methotrexate, azathioprine, cyclophosphamide, or irradiation are reserved for those patients who remain refractory or continue to progress despite treatment with corticosteroids [44].

Conclusion

The discovery in 1970 of antibodies directed against the acetylcholine receptor in patients with myasthenia gravis finally provided a rationale for treatment directed at the underlying problem, and dramatically improved survival and quality of

life. The discovery a couple of decades later of autoantibodies in Lambert-Eaton myasthenic syndrome similarly provided treatment strategies beyond the merely symptomatic. Continued advances in immunologic knowledge have allowed for advances in diagnostic testing and new treatment options in the inflammatory diseases of muscle as well. Inclusion body myositis, however, remains stubbornly obdurate to our understanding and to effective treatment. Chronic inflammation as a factor in progressive weakness in muscular dystrophy offers opportunities for therapeutic advances. Further randomized, placebo-controlled trials are important to best determine the most effective treatments for these immune-mediated disorders.

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