A Physician's Guide to Myositis

THE MYOSITIS ASSOCIATION

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Overview

Myositis encompasses a phenotypically heterogeneous collection of rare diseases also referred to as idiopathic inflammatory myopathies or autoimmune myopathies. These myopathies, which affect 50,000-70,000 people in the United States, include polymyositis, dermatomyositis, juvenile myositis, sporadic inclusion body myositis, and myositis in overlap with another systemic autoimmune rheumatic disease. Polymyositis, dermatomyositis, juvenile myositis, and the overlap syndromes are autoimmune disorders, whereas inclusion body myositis has features of both autoimmunity and muscle fiber degeneration.[1] An additional subset of myositis has been distinguished recently known variously as necrotizing myopathy, immune-mediated necrotizing myopathy, or necrotizing autoimmune myopathy.

These diseases typically involve symmetrical proximal muscle weakness, elevated serum muscle enzymes such as creatine kinase (CK), myopathic changes on electromyography, and a set of typical histological patterns on muscle biopsy, which include the presence of inflammatory cell infiltrates in muscle tissue. Some myositis is also strongly associated with cancer.[2] If left untreated, myositis can cause significant morbidity and even death.

A number of myositis-specific or associated autoantibodies have been identified to define patient subgroups, guide treatment, demonstrate an increased risk of malignancy, and support prediction of outcomes. Proinflammatory cytokines, such as interleukin 6 and type 1 interferon-dependent genes, may also serve as potential biomarkers of disease activity in adult and juvenile forms of dermatomyositis. Magnetic resonance imaging has become important in assessing muscle inflammation in adult and juvenile myositis. Much confusion remains, however, over how to effectively manage patients with myositis, since there have been few large-scale, randomized, controlled studies.[3]

Epidemiology and Clinical Manifestations

Polymyositis, dermatomyositis, juvenile myositis, overlap disorders, and necrotizing myopathy

Polymyositis (PM) and dermatomyositis (DM) typically occur in adults with a median age of 49, although PM can begin as early as the late teens. Females outnumber males by a 2 to 1 ratio.

Necrotizing myopathy (NM) is clinically similar to PM but is histologically distinct from both PM and DM. It usually occurs following exposure to cholesterol-lowering statin medications, but, unlike typical statin-induced myopathy, it persists even after the drug is withdrawn. However, NM is extremely uncommon and up to 30% of patients with NM have never received a statin agent. Yet, it is estimated that 5–20% of patients taking statin medications are affected by symptoms of myalgia and mild serum CK elevation. Rhabdomyolysis requiring discontinuation of these drugs is also quite rare.[4]

Juvenile myositis (JM) begins in childhood or the teen years. The mean age of onset for juvenile dermatomyositis (JDM) is seven years, with peaks for girls between 6 and 11 years. JDM is extremely rare in boys over the age of 9. Juvenile polymyositis (JPM) usually develops several years later. The overall female-to-male ratio is 1.7 to 1. The incidence in African American children is similar to that in Caucasian children.

Patients with PM, DM, JM, overlap disorders, and NM usually present with symmetric weakness of proximal muscles that develops subacutely, over weeks to months. Patients have difficulty in standing from a seated position, climbing stairs, or performing activities that require them to raise their hands over their heads. In patients with more severe disease, distal weakness can occur, neck flexor weakness can lead to head drop, pharyngeal muscle weakness can result in dysphagia and/

or dysphonia, and diaphragm involvement can cause respiratory compromise. Myalgia is more common in DM, perhaps as a result of fasciitis rather than myositis.[5]

On physical examination, muscle weakness is predominantly noted in the deltoids, biceps, triceps, hip flexors, quadriceps, and hamstrings. Other features that may be present include fever, dyspnea (due to interstitial lung disease, aspiration, diaphragm weakness, or cardiomyopathy), arthralgia, arthritis, and Raynaud's phenomenon. Patients with overlap myositis may also have symptoms of other connective tissue diseases, such as systemic lupus erythematosus, scleroderma, Sjögren's disease, or mixed connective tissue disease.

The most significant distinguishing feature of DM—one that has a significant negative impact on patients' quality of life—is the presence of cutaneous involvement. Skin changes can precede, coincide with, or develop after the onset of muscle weakness. Indeed, some patients with the skin symptoms of DM present with little or no muscle disease, which is referred to as hypo- or amyopathic dermatomyositis.

The most characteristic cutaneous manifestations of DM include a heliotrope eruption (pink to violaceous erythema of the eyelids, occasionally with associated edema); Gottron's papules (raised erythematous to violaceous papules or plaques on the extensor surfaces of the metacarpophalangeal and interphalangeal joints); and Gottron's sign (erythematous to violaceous macules on the elbows, knees, and lateral malleoli).[6]

In addition to these classic clinical findings, other skin manifestations include erythema and/or poikiloderma in a photosensitive distribution. Typical sites include the midface (which can mimic the malar rash of systemic lupus erythematosus, but involves the nasolabial folds instead of sparing these sites), the anterior neck and chest (V sign), and the posterior neck and shoulders (shawl sign).

In addition to photosensitivity, cutaneous disease in DM is often associated with intense pruritus. Scalp involvement can lead to both pruritus and hair loss. Some cutaneous lesions of dermatomyositis can ulcerate and become necrotic. Additional changes that may occur on the hands include periungual erythema, cuticular overgrowth,

nailfold capillary changes (dilated capillary loops and drop out of nailfold capillaries), and hyperkeratosis and fissuring of skin on the lateral and palmar aspects of the fingers and hands (mechanic's hands). These rashes can occur alone or in combination. Raynaud's phenomenon is also common, especially in patients testing positive for anti-Jo-1 autoantibodies.

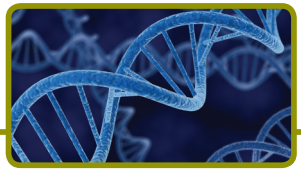
In addition to these symptoms seen in adults with PM, DM, overlap disorders, and NM, children may experience symptoms that are rarely observed in adults. Subcutaneous calcification (dystrophic calcinosis) occurs more frequently in children, particularly among those in whom initiation of therapy is delayed or those in whom the disease is poorly controlled with medication. Gastrointestinal symptoms also occur and include abdominal pain, hematemesis, or melena. These are the result of bowel infarction or perforation caused by a vasculopathy or vasculitis. Finally, children may develop lipodystrophy, with generalized or focal loss of subcutaneous or visceral fat.

Sporadic inclusion body myositis

Sporadic inclusion body myositis (sIBM) is a disease of older individuals, with onset prior to age 45 years being very rare. This disease is three times as common in males as females. Indeed, sIBM is the most common acquired myopathy in men over the age of 50.[7]

Patients with sIBM typically present with both proximal and distal muscle weakness that is asymmetric in distribution. A common pattern of weakness involves the triceps, wrist flexors, distal finger flexors, quadriceps, and ankle dorsiflexors. This is a progressive degenerative disease. Weakness generally develops very slowly over months to years, and the longer the weakness persists, the more atrophy will be apparent. Dysphagia is common in patients with sIBM, but other extramuscular findings that can occur in PM and DM are not seen. While the weakness in sIBM does not affect life expectancy, over the years, it can cause significant disabling weakness, requiring adaptive equipment for mobility and impacting the quality of life. Dyphagia, resulting in aspiration pneumonia, is one of the leading causes of morbidity and mortality in sIBM patients.

Pathogenesis



Polymyositis, dermatomyositis, and necrotizing myopathy

The causes of the various forms of myositis are unknown. Several studies indicate environmental exposure to such triggers as infections agents, toxins (usually drugs), ultraviolet radiation, or combinations of these mechanisms may lead to autoimmune dysfunction in genetically susceptible individuals.[8] In addition to these autoimmune inflammatory mechanisms, NM and some forms of DM are also believed to result from paraneoplastic conditions.[9] Autoimmunity is strongly implicated because patients with these forms of myositis often have circulating autoantibodies and they respond to immunosuppressive therapies.

The most likely environmental triggers implicated in idiopathic inflammatory myopathies are infections. The onset of these diseases often coincides with an infection, and viruses are strong candidates. Enteroviruses can cause a self-limited myositis in children. Retroviruses, human immunodeficiency virus (HIV), and human T-cell lymphoma virus-1 (HTLV-1) can cause myositis. Several viruses can induce various forms of myositis in laboratory animals. High titers of anti-viral antibodies have been found in patients' serum. Other infectious agents implicated include certain bacteria and the parasite toxoplasma gondii.

Medications may also serve as a trigger. D-penicillamine can cause DM. Statin drugs can cause a NM that has the clinical phenotype of PM.[10] Many patients with this myopathy have circulating antibodies to 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and respond to intensive immunosuppressive therapy. Other myotoxic medications implicated include zidovudine (AZT), hydroxyurea, colchicine, hydroxychloroquine, amiodarone, interferons, L-tryptophan, and growth hormone. In addition, anti-tumor necrosis factor agents have also been implicated in inducing or exacerbating DM and PM.

Dermatomyositis uniquely involves capillary ischemia, which is thought to be related to a vascular inflammatory process with extravasation of immune cells into the muscle tissue.[9] Chronic immune vascular damage and insufficiency in DM may cause ischemia, myofiber atrophy, and capillary damage in "watershed" regions of muscle near the avascular perimysium.[11]

Ultraviolet light also appears to be a factor in the development of DM. The ratio of DM to PM is directly correlated with exposure to ultraviolet light, the ratio being highest near the equator and becoming lower farther away from the equator. Thus, it has been postulated that ultraviolet light may trigger DM or serve as an exogenous factor that could modify the clinical phenotype of DM versus PM.[12]

Patients with DM are at increased risk for developing malignancy, especially in individuals over the age of 40 years.[13] When the two coincide, treatment or removal of the malignancy may lead to improvement or remission of the myositis. The pathophysiologic link between the two conditions is unclear. The association of the onset of the two, usually within one year of each other, suggests that DM may be the consequence of the malignancy or that the two share a common mechanism of disease. Thus, an autoimmune response directed against a malignancy may cross-react with regenerating muscle leading to myositis, or vice versa.[14]

Sporadic inclusion body myositis

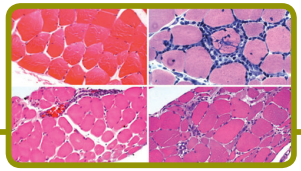
Although inflammatory cells are found in the muscle tissue of patients with sIBM, especially earlier in the disease process, their role in causing muscle weakness is unclear. And while autoantibodies have been found in patients with sIBM, the weakness appears to be the result of a myodegenerative process, because, unlike the other forms of myositis, sIBM does not respond to immunosuppressive therapy.

As with PM, sIBM is a T-cell mediated disorder in which CD8 positive cytotoxic T cells invade muscle fibers, leading to necrosis.[15] Evidence has also been found to suggest that defects in neurodegenerative pathways may confer genetic susceptibility to this form of myositis.[16]

In addition, a circulating autoantibody directed at cytosolic 5' nucleotidase 1A, an enzyme involved in purine nucleotide breakdown, has been found in up to half of sIBM patients,[1] creating speculation that binding of this autoantibody to its antigen could lead to abnormal nucleic acid metabolism, resulting in muscle fiber degeneration.

Researchers are as yet unclear about these apparently conflicting pathologic features (i.e. inflammation and protein aggregation) and their roles in disease pathogenesis. It is likely that any future therapy will need to target both aspects of sIBM pathologies.[17]

Diagnostic Criteria and Differential Diagnosis



Diagnosing inflammatory myopathies revolves around a pattern of abnormalities found through physical examination, laboratory evaluation, imaging studies, multidisciplinary consultations, histologic examination, and possibly genetic studies.

These abnormalities include muscle weakness, elevated serum levels of skeletal muscle enzymes, myopathic changes on needle electromyography (EMG), and inflammatory changes in muscle tissue observed through magnetic resonance imaging or muscle biopsy.[18] None of these abnormalities is specific or unique to myositis. Furthermore, not all patients will manifest all of these findings. Therefore, other causes for these abnormalities must be excluded before rendering the diagnosis of one or another form of myositis.

Additionally, some myositis specialists believe PM is overdiagnosed. Clinical manifestations often make it indistinguishable from NM or early sIBM. Muscle biopsy and an autoantibody profile can be helpful in the diagnostic process.[9]

Physical examination

Physical findings include any of the clinical manifestations identified above.

Muscle enzymes

Elevated serum levels of enzymes derived from skeletal muscle are usually an indication of active muscle disease or injury. These enzymes include creatine kinase (CK), aldolase, alanine transaminase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH). All or any combination of these can be elevated in an individual patient. CK is the enzyme most commonly tested and followed and is elevated in the vast majority of patients at presentation. Normal values are more likely to be

encountered in patients with DM than in PM or NM. The increase in level ranges from 1.5 to 20 times the upper limit of normal.

Needle electromyography (EMG)

The changes reported on needle EMG in patients with active PM, DM, or NM include polyphasic motor units of low amplitude and short duration (myopathic motor units); fibrillations and positive sharp waves; and bizarre, repetitive discharges. These myopathic changes are characteristic of inflamed muscle but are not specific. Only 40% of patients will have all of these changes. In 10%, EMGs are entirely normal. This may be due to sampling error because not all muscles are affected in these diseases; muscles showing EMG abnormalities are those that are inflamed and are clinically weak, whereas those lacking EMG abnormalities usually show no inflammation. Patients with sIBM may also have some changes that are considered neuropathic.

Magnetic resonance imaging (MRI)

Findings of edema in skeletal muscle on MRI are a strong indicator of inflammation and are suggested by increased signal on T2 and STIR sequences or by gadolinium enhancement.

MRI is also an excellent method for localizing the site for muscle biopsy to make certain the specimen is taken from an abnormal area. The presence of edema in muscle in a pediatric patient with proximal muscle weakness, elevated muscle enzymes, and myopathic changes on EMG may obviate the need for muscle biopsy.

Additionally, MRI helps identify the pattern of muscle involvement. In sIBM patients, a forearm muscle MRI may highlight the preferential involvement of the forearm flexor compartment that correlates to the selective finger flexor weakness seen in sIBM patients (and not in DM or PM).

Muscle biopsy

Histology of skeletal muscle in classic PM reveals degenerating and regenerating muscle fibers with CD8+ T cells invading and

surrounding muscle fibers. In contrast, in DM, perifasicular atrophy is observed, and the invading inflammatory cells are CD4+ lymphocytes, plasmacytoid dendritic cells, and B lymphocytes localized to perivascular areas.

Muscle biopsy in NM shows necrotic muscle fibers without significant lymphocytic inflammatory cell infiltration. Perifascicular atrophy is also lacking.

Sporadic inclusion body myositis may demonstrate similar endomysial inflammatory changes to those seen in PM, although milder; the finding of rimmed or lined vacuoles or inclusions in muscle fibers containing basophilic granular material can be diagnostic. In addition, histochemistry can reveal angular atrophic muscle fibers and fiber type grouping, signs of denervation and reinnervation, respectively.

In some patients the findings are far from classic, showing nonspecific myopathic changes. In others, the biopsy can be normal. This is, again, believed to be the result of sampling error due to the heterogeneous or patchy distribution of changes within various muscles.

Skin biopsy

Histopathology of skin biopsies from patients with DM shows perivascular inflammation, hyperkeratosis in the stratum corneum, epidermal atrophy, follicular plugging, and interface dermatitis (inflammatory cells at or obscuring the dermal-epidermal junction). These changes are not specific for DM, because they can also be seen in systemic lupus erythematosus.

Differential diagnosis

Because the criteria used to establish the diagnosis of a particular form of myositis are nonspecific, patients with other diseases may fulfill them. The list of diseases that can cause muscle weakness, elevated muscle enzymes, myopathic EMG findings, and/or myopathic changes on muscle biopsy is extensive.

Primary neuropathic disorders that can mimic inflammatory myopathies include amyotrophic lateral sclerosis, chronic spinal muscular atrophy, and myasthenia gravis. The limb-girdle and facioscapulohumeral muscular dystrophies not only cause proximal muscle weakness, elevated enzymes, and myopathic EMG changes, but also can have inflammatory infiltrates in muscle biopsies early in their course. Myophosphorylase deficiency (McArdle's disease), acid maltase deficiency, and mitochondrial myopathies are metabolic disorders that should be considered.

Endocrinopathies such as Cushing's syndrome, hypothyroidism, hyperthyroidism, hyperparathyroidism, and acromegaly must be ruled out. The inflammatory myopathy that occurs in HIV or HTLV-1 infections is indistinguishable from PM. Statins, alpha-interferons, and some medications used to treat HIV infections can lead to muscle involvement and clinical confusion. Muscle biopsies from patients with myopathies caused by colchicine, hydroxychloroquine, or alcohol may show vacuoles in the muscle fibers and can thus be confused with IBM.

Hereditary inclusion body myopathies (hIBM) should not be mistaken for sIBM. Although the hIBMs share some of the pathologic changes observed in sIBM—lined or rimmed vacuoles on histology and tubular inclusions on electron microscopy—these conditions are otherwise quite different. The hereditary form of the disease is caused by an autosomal dominant or recessive gene. While sIBM is a disease of aging, the average age of onset in hIBM is between the teenage years and mid-twenties. The muscle weakness in hIBM is usually distal and may be accompanied by ophthalmoplegia, brain white matter disease, or bulbar weakness. CK levels range from normal to slightly elevated. EMG results are normal. Finally, there is no inflammation in muscle tissues in the hereditary form.

Some skin conditions may mimic the dermal changes seen in DM in both children and adults. The facial erythema and other photosensitive eruptions characteristic of systemic lupus erythematosus (SLE), for example, may resemble some of the facial changes seen in DM. Psoriasis or seborrheic dermatitis involving the scalp may resemble scalp DM.

Treatment Guidelines

Glucocorticoids form the foundation for the treatment of NM, PM, DM (adult and juvenile), and the overlap myositis disorders. Depending on the severity of disease at the time of diagnosis, they may be initiated as a single agent or in combination with other immunosuppressive agents. Most initial doses are the equivalent of 1 to 2 mg/kg per day of prednisone, although some advocate pulsing initially with high dose intravenous methylprednisolone in the setting of more severe disease. Regardless, high doses are usually maintained for 6 to 12 weeks or more, until the strength nearly normalizes or the slope of improvement plateaus. If a patient responds dramatically (for example, in one to two weeks) it is likely that the patient has an overlap disorder with another rheumatic disease such as systemic lupus erythematosus. Premature tapering of the steroids may result in an incomplete response or an exacerbation of muscle weakness.

Many other second-line immunosuppressive agents have been employed to treat PM, DM, NM, JM, and overlap disorders. Few of these agents have been tested in rigorous randomized controlled trials, though general expert consensus confirms their use. Agents that have demonstrated efficacy in clinical trials include methotrexate, azathioprine, and intravenous immune globulin (IVIg). These medications are often used in addition to glucocorticoid therapy as a means of reducing the steroid dose.

Evidence for other immunosuppressive therapies is derived mainly from uncontrolled studies. Cyclosporine and tacrolimus have shown efficacy in myositis including those patients with interstitial lung disease (ILD). Mycophenolate mofetil is effective in PM, refractory DM, and those with ILD. Many controlled and uncontrolled studies using rituximab are encouraging, including its efficacy in ILD. Anti-tumor necrosis factor (TNF) agents have shown mixed results in small, randomized clinical trials with infliximab demonstrating no benefit and etanercept leading to encouraging results warranting further study.[19]

Some newer novel therapies such as tocilizumab, arimoclomol, abatacept, and IMO-8400, an antagonist of toll-like receptors, are currently under investigation.

ACTH gel is the only medication, other than glucocorticoids, that the FDA has approved for the treatment of PM or DM.[20] It is now recognized that ACTH has anti-inflammatory and immunomodulatory activities in addition to stimulating cortisol production by the adrenal cortex.

Regardless of the agent, the sooner in the course of the disease that safe and effective treatment is initiated, the better the chance for a successful outcome. Unfortunately, there are patients who do not achieve remission. When that happens, several questions should be addressed. Was the immunosuppressive dosing high enough or long enough? Could the concomitant development of steroid myopathy complicate the picture? In adults with DM, could they have an associated malignancy? If these potentials can be eliminated, then it is possible that the patient either has a refractory form of disease (anti-SRP antibody-positive PM or sIBM) or the diagnosis of myositis is inaccurate.

Treatment of skin disease in DM can be particularly challenging. All patients with adult or juvenile DM should be counseled regarding strict photoprotection, because sun exposure is known to exacerbate the skin disease. In addition, topical corticosteroids, topical calcineurin inhibitors, and antimalarial agents are often given to improve skin disease and alleviate the associated pruritus. Many patients with refractory skin disease require additional therapies, such as methotrexate, mycophenolate mofetil, or IVIg, among others.

While PM, DM, JM, overlap disorders, and NM all, to varying degrees, are responsive to immune suppression and other therapies, sIBM remains intractable. To date, there is no proven effective treatment that will reverse the progressive muscle weakness and debilitation of this form of myositis.

Nevertheless, research continues to better understand sIBM and to seek a treatment. A recent study of bimagrumab, a human monoclonal antibody developed to treat pathological muscle loss and weakness, demonstrated increase in muscle mass; however, this did not translate to functional improvement in strength. AAV1-FS344, a gene therapy-delivered follistatin protein that increases muscle strength and function, has been shown to improve walking ability in patients with Becker muscular dystrophy and is currently being studied in patients with sIBM.

Prognosis

The heterogeneity of the idiopathic inflammatory myopathies, even within the clinically distinguished forms, has made it difficult to describe disease progression and outcomes with certainty. Difficulties in coming to an accurate diagnosis and initiation of effective treatment decrease the chances of positive outcomes.

To a large extent, prognosis is relative to the presence of other co-morbid conditions, such as ILD or malignancy, and complications, such as infection as a side effect of immunosuppressive treatment. Associations that have been made with certain autoantibody profiles, however, have led to our most reliable predictions of outcomes.

Five-year survival rates for those with PM, DM, and NM is greater than 95%. About 40% of adults will have a monophasic illness and do very well. The vast majority of individuals in this group will be left with no functional disability. About 20% of patients have a remitting and relapsing course, while the remainder will have a chronic progressive disease.[21] A rare number of patients, however, experience a severe acute onset of symptoms, which if not treated immediately and aggressively, can lead to death.

The cutaneous manifestations of DM may or may not improve with therapy in parallel with the improvement of the myositis. In some patients, the weakness and rash resolve together. In others, the two are not linked, with one or the other being more challenging to control. Often, cutaneous disease persists after adequate control of the muscle disease.

About 60% of children with myositis have a monophasic illness, with the remainder having a remitting and relapsing course or progressive disease. However, between 65% and 80% have a normal to good functional outcome. Approximately 5% become wheelchair dependent.[22] The mortality rate is 1% to 2%. Risk factors for poor prognosis include unremitting severe disease, dysphagia, dysphonia, vasculopathy, and circulating anti-SRP

antibodies. Delay in initiation of therapy is also associated with poor prognosis and with the development of subcutaneous calcifications. Of note, children with JDM do not have an increased risk of malignancy.

While patients with sIBM experience a steady degenerative course resulting in the poorest functional outcomes, they nevertheless have the best survival rate. The mean decline in muscle strength is slow but persistent at 3.5% to 5.4% per year. This results in the majority of individuals becoming completely wheelchair dependent. Life expectancy, however, is normal at 81 years.[23]

Autoantibodies and myositis

A number of antibodies have been identified in myositis patients that are rarely found in other diseases. The presence of these myositis-specific autoantibodies (MSAs) are not only diagnostic but can predict disease outcomes.

Other autoantibodies, known as myositis-associated autoantibodies (MAA), have also been identified. These autoantibodies are found in patients with myositis, but they are also present in patients with other autoimmune diseases such as scleroderma and systemic lupus erythematosus. While they are not diagnostic, the presence of these autoantibodies may be helpful in determining treatment and outcomes.

Autoantibodies—either MSAs or MAAs—can be found in more than 80% of patients with PM or DM[24] and about 60% of JDM patients.[25] These biomarkers are less common in sIBM, however recent research has identified anti-cN-1A as a biomarker for sIBM with 33% of IBM patients positive for the autoantibody.[26]

Similarly, autoantibodies to the cholesterol regulating enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) have been identified as a marker for NM. Two-thirds of myositis patients exhibiting these autoantibodies have previously been exposed to statin medications. These patients tend to have a chronic disease requiring long-term immunosuppression. Younger patients tend to have more severe disease and a worse prognosis than older patients.[27]

The presence of certain MAAs indicates an association with another systemic autoimmune rheumatic disorder. For example, the presence of anti-double stranded-DNA antibodies may point to systemic lupus erythematosus, whereas the presence of anti-Scl-70 antibodies may indicate scleroderma as the associated rheumatic disorder.

In general, the autoantibody status helps to predict outcomes. Dozens of myositis-specific and myositis-associated antibodies have been identified in recent years, and researchers are learning more about them. See Table 1.

Table 1.

MSAs and clinical features associated with them

		Autoantibody frequency, %	
Autoantibodies	**Clinical features**	**Adult IIM**	**JM**
Anti-ARS	Anti-syn syndrome with moderate to severe muscle weakness, high muscle enzyme levels, RP, mechanic's hands, fevers, arthritis, and ILD	30–40	<5
Anti-Jo-1	Chronic continuous disease course, with clinical symptoms for > two years after diagnosis; mean five-year survival rate = 65%, usually due to ILD; anti-Syn syndrome features	20	
Anti-PL-7	Anti-syn syndrome with higher frequency of ILD	5	
Anti-PL-12	Anti-syn syndrome with higher frequency of ILD	5	
Anti-EJ	Dermatomyositis and ILD	<5	
Anti-OJ	Myositis and ILD	<5	
Anti-KS	ILD with less myositis	<1	
Anti-Ha	NA	<1	
Anti-Zo	Myositis and ILD	<1	

		Autoantibody frequency, %	
Autoantibodies	**Clinical features**	**Adult IIM**	**JM**
Anti-SRP	Acute onset necrotizing myopathy with severe weakness, high CK, cardiac involvement; refractory to treatment; 5-year survival rate = 30% (some series)	5	<1
Anti-Mi-2	Adult DM and JDM with hallmark cutaneous disease, milder myositis with good response to treatment	<10	<10
TIF1-g (Anti-p155/140)	CAM in adult DM; severe cutaneous disease in adult DM and JDM	13–21	23–29
Anti-SAE	Adult DM; may present with CADM first	<5	NA
Anti-MDA5 (anti- CADM-140)	CADM; rapidly progressive ILD	5	Unknown
Anti-NXP-2	Predominantly JDM with subcutaneous edema, calcinosis, and a severe muscle phenotype with contractures; increased risk of cancer in some adult DM studies	<5	13–23
Anti-HMGCR	NM; associated with statin use in adults; severe proximal muscle weakness; partially responsive to immunosuppressive medications; better response to IVIg	<5	NA
cN-1A (Mup44, NT5c1A)	IBM; higher mortality risk	33% of IBM	NA

ARS=aminoacyl-tRNA synthetase; Anti-Syn syndrome=antisynthetase syndrome; RP=Raynaud's phenomenon; ILD=interstitial lung disease; SRP=signal recognition particle; TIF1-γ=transcriptional intermediary factor 1-gamma; NXP-2=nuclear matrix protein NXP-2; SAE=small-ubiquitin-like modifier activating enzyme; MDA5=melanoma-differentiation associated gene 5; CAM=cancer-associated myositis; CADM; clinically amyopathic DM; NA=not applicable/no data.

Complicating Conditions

Dysphagia

Although PM and DM typically manifest as progressive skeletal muscle weakness, symptoms involving systems not related to skeletal muscles are common and can be even more clinically significant than the myositis itself. Dysphagia affects patients with pharyngeal muscle dysfunction. Aspiration pneumonia due to dysphagia occurs in 17% of patients with PM and DM and, along with hypoventilation and atelectasis, can be potentially fatal.[28]

Patients with dysphagia may have difficulty swallowing or experience choking, coughing, and heartburn. They may lose weight and develop nutritional deficiencies, which will exacerbate their muscle weakness.

Early recognition of dysphagia is key, and evaluation of swallowing difficulties should be part of the initial assessment and follow-up. If dysphagia is suspected, further evaluation should include barium swallow, endoscopy, and/or other imaging studies. Symptoms are often worse at night and are exacerbated by comorbid conditions such as lung disease and sleep apnea.

Antisynthetase syndrome

Antisynthetase syndrome is a distinct clinical entity that is characterized by the presence of anti-aminoacyl-tRNA synthetase (anti-ARS) autoantibodies, myositis, ILD, fever, arthritis, Raynaud's phenomenon, and cracking and fissuring of the lateral aspects of the fingers (also referred to as mechanic's hands). Anti-Jo-1 is the most common of the antisynthetase antibodies associated with myositis. Other anti-ARS antibodies have been described that often involve a clinical phenotype different from that seen in patients with anti-Jo-1 antibodies and may involve a lower incidence of myositis and a higher incidence of ILD. Myositis symptoms are not universally present in patients with antisynthetase syndrome.

Interstitial lung disease is the most common non-musculoskeletal manifestation in patients with PM and DM. Up to 75% of patients who present with PM and DM have evidence of ILD. The presence of anti-ARS antibodies is a biomarker for ILD. Myositis patients who present with respiratory symptoms should always be assessed for ILD.[28]

For many patients with ILD, the onset of dyspnea is insidious, occurring over a period of months. Other patients, however, experience a more severe, acute onset of ILD, fever, and dyspnea, progressing over a period of days or weeks and requiring aggressive initial treatment.

Diagnostic studies include chest x-ray, high resolution CT scans, and lung biopsy. These typically reveal a pattern of nonspecific interstitial pneumonia, with or without areas of consolidation. Many patients also present with a distinct pattern of reticular and ground-glass opacities, with decreased lung volume, traction bronchiectasis, and scattered areas of consolidation that is highly suggestive of antisynthetase syndrome-related ILD.

Differential diagnoses include infection, heart disease, medication side effects, pneumonitis, and non-skeletal myositis muscle involvement.

Immunosuppressive therapy is the treatment of choice, using a combination of glucocorticoids and a steroid-sparing agent (mycophenolate mofetil or azathioprine). Cyclophosphamide can be used for severe cases with rapidly progressive ILD. Rituximab and tacrolimus have also been used for patients resistant to aggressive conventional therapy.

Rhabdomyolysis

Rhabdomyolysis is a serious complication that occurs as a result of skeletal muscle damage and the rapid release of intracellular contents into the circulation. Presentation varies considerably, but major symptoms include myalgia, generalized weakness, and darkened urine due to myoglobinuria. Other nonspecific symptoms include fever, nausea, and vomiting.

Creatine kinase levels are very elevated, and depending on the severity of illness patients may demonstrate a range of laboratory findings, including electrolyte imbalances and acute kidney injury.

In rhabdomyolysis due to myositis, the patient's history may not include the trigger events typical for rhabdomyolysis such as trauma, crushing injury, prolonged immobilization, drug use, and others. Indeed, with the exception of darkened urine, most of the above symptoms do not differentiate this complication from other symptoms of inflammatory myopathy. Nevertheless, in rare cases, patients presenting with severe, acute-onset of PM or DM may suffer severe morbidity and even death in part as a result of rhabdomyolysis.

In addition to treating the myopathy with aggressive immunosuppression, treatment of rhabdomyolysis includes generous intravenous hydration, management of electrolyte balance, monitoring of heart and kidney function, and muscle rest.

Cardiovascular disease

Clinically significant cardiac involvement is uncommon in inflammatory myopathies, but heart disease is nevertheless one of the major causes of death in patients with PM, DM, and JM. Traditional cardiovascular risk factors (including diabetes, hypertension, dyslipidemia, obesity, and smoking) are more prevalent in adults with myositis, and the risk of developing atherosclerotic coronary artery disease is increased twofold to fourfold in myositis patients over that of the general population.

Researchers speculate that interactions between proinflammatory cytokines and traditional cardiac risk factors may contribute to the pathogenesis of heart disease in patients with myositis. It is also possible that cardiac involvement could be related to myocarditis and/or myocardial fibrosis, leading to arrhythmias and congestive heart failure. Reduced heart rate variability, which is a known risk factor for cardiac morbidity and mortality, has been demonstrated in patients with long-standing JDM.[29]

New diagnostic techniques have also revealed a high incidence of subclinical cardiac involvement, especially diastolic dysfunction.

Subclinical cardiac pathology may indicate the early stages of cardiac remodeling that will later manifest as clinical heart disease. Patients with myositis should, therefore, follow the same recommendations for cardiovascular risk assessment and prevention as those for all patients. A low threshold should also be given to cardiac workup and follow up in patients with myositis, including children.

Of special note: Statin drugs, now widely used to lower cholesterol, have also demonstrated muscle pain and weakness as a side effect of treatment in as many as 5% of patients. Myositis patients who use these drugs may experience worsening of muscle symptoms that may mimic myositis relapse. Statins are also causally implicated in the development of NM.

Ongoing Management

Infection

In addition to the serious side effects of long-term immunosuppressive therapies, immunosuppressed patients are at high risk for infection. Patients and caregivers should be instructed on the importance of avoiding contact with those with communicable diseases, frequent handwashing, and wellness behaviors that can help prevent infections. They should also understand the signs of infection and the importance of seeking medical attention promptly. Appropriate immunizations should also be administered, avoiding live vaccines.

Screening for malignancy

Relative to the general population, middle-aged and elderly patients with DM and PM are at a significantly greater risk for developing a malignancy. By some estimates, those with DM are six times more likely to develop cancer; those with PM are twice as likely. The type of cancer found in these patients generally reflects the types of cancer found within populations of the same origin, age, and gender.[30]

Observational data suggest that the association of cancer and myositis is not coincidental. Patients sometimes develop myositis around the time they are diagnosed with cancer. Patients with DM experience improvement in rash and muscle strength when their cancer is treated. And when tumors recur, muscle weakness often returns as well.

A diagnosis of DM or PM, therefore, requires evaluation for malignancy. In addition to a thorough history and physical examination, including a gynecologic exam for women, these patients should also receive ongoing, age-appropriate cancer screening. Whole-body positron emission tomography (PET)/

CT has been suggested as a cancer screening tool. Alternatively, CT scans of chest, abdomen, and pelvis are indicated, and women should be assessed for ovarian cancer with transvaginal pelvic ultrasound and tumor marker analysis. Recent studies have also shown a promising role of anti TIF1-gamma autoantibody to exclude the presence of occult malignancy with a high negative predictive value.[31]

Exercise

A growing body of research has shown that regular exercise is not only safe for patients with all forms of myositis, but it also can reduce disease activity, inflammation, impairment, and activity limitation. Exercise can also improve strength and function, muscle metabolism, and aerobic capacity of muscle. Even intensive aerobic exercise and resistance training is possible. All forms of exercise contribute to improved quality of life.[32]

Exercise programs should be tailored for each individual, beginning with low intensity and progressing slowly to tolerance. One approach is to have the patient do aerobic exercise every other day three times a week alternating with anaerobic exercise for the alternate three days, then one day of rest.

Adjunct therapies

The value of a healthy lifestyle and diet should not be underestimated. Smoking cessation, moderate alcohol consumption, regular exercise, maintaining a healthy weight, and eating a healthy diet are among the lifestyle changes that can have a significant impact on health and wellbeing.

Many myositis patients find that their symptoms improve when they follow what is referred to as an “anti-inflammatory diet.” This healthy eating plan emphasizes fresh fruits and vegetables, mushrooms, whole grains, beans and legumes, nuts, and fish and seafood. It favors organic foods and strictly avoids high fructose corn syrup, hydrogenated oils and fats, and processed and fast foods. And it recommends decreased consumption of animal proteins in favor of vegetable sources and high quality dairy products.

Other lifestyle ideas to consider include stress management, developing satisfying social relationships, getting enough sleep, developing an attitude of gratitude, engaging in creative pursuits, living with purpose, staying intellectually engaged, and maintaining positive mental health. Meditative practices, including yoga and prayer, have also been shown to have a beneficial impact on health.

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Founded in 1993, The Myositis Association is the leading international support and educational organization for people with myositis, including polymyositis, dermatomyositis, and inclusion body myositis. A non-profit organization based in Alexandria, Virginia, TMA provides patient education and advocacy, facilitates patient support groups, hosts an annual patient conference, engages the medical community in educating physicians about these rare diseases, and funds medical research into the causes, treatments, and possible cures for myositis.

TMA offers the following resources and support for physicians who treat people with myositis.

- A Physician's Guide To Myositis – available in print and online
- Office brochures for patients – available in print and online
- Periodic email updates with news about TMA services and new research
- Professional consultation and connection with TMA's Medical Advisory Board
- Fellowships and research support for physicians and scientists engaged in myositis research
- Grand Rounds programs featuring TMA medical advisors at medical schools in the US
- A yearly medical symposium in which TMA medical advisors share and discuss their current research with members of the medical community
- TMA participation in worldwide research collaborations charged with advancing the understanding of myositis
- Outreach to primary care and specialty practitioners to acquaint them with diagnosis and treatment of myositis

More information about these programs and services is available at tma@myositis.org or 800-821-7356.

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