Inflammatory myositis is classified as (1) idiopathic polymyositis, (2) idiopathic dermatomyositis, (3) dermatomyositis and polymyositis associated with malignancies, (4) childhood dermatomyositis or polymyositis, (5) dermatomyositis or polymyositis associated with connective tissue diseases, (6) inclusion body myositis, and (7) miscellaneous; eosinophilic myositis, myositis ossificans, focal myositis, infectious myositis, and giant cell myositis.

Polymyositis and dermatomyositis share many clinical features. Both have proximal muscle weakness, elevated muscle enzymes, characteristic EMG and muscle biopsies, are associated with malignancies and have a female to male ratio of 2 to 1 and are more common in African Americans than Caucasians. Both are seen in children although polymyositis is quite rare in children. Dermatomyositis is polymyositis with specific dermatologic manifestations and distinct muscle biopsy features. The characteristic dermatologic features of dermatomyositis are Gottron's papules, shawl or V-neck rash, rash over the extensor surfaces and calcinosis cutis. Gottron's papules look like flat warts over the knuckles on erythematous base. Inclusion body muscle disease is primarily a disease of older males, greater than 50 years of age, with asymmetric, distal muscle disease with neurologic features. It is unresponsive to therapy.

Immunopathology—Polymyositis is a cell-mediated autoimmune disorder in which cytotoxic (CD8-positive) lymphocytes and macrophages invade and destroy myofibers expressing MHC-I antigens. The inflammatory cells are in the endomysium (between and around individual myofibers.) Inflammation may be focal and the MRI is useful in identifying affected areas for biopsy.

The pathology of dermatomyositis includes inflammation, vasculitis, and perifascicular atrophy. The inflammatory cells are predominantly B-cells (with smaller numbers of CD4-positive T-cells) and are found around blood vessels, in the septa between muscle fascicles, and in fibroadipose tissue around muscle. The key pathological change of dermatomyositis is vasculitis, which involves endomysial and perimysial capillaries and arterioles. This vasculitis begins with endothelial swelling and is followed by endothelial necrosis and capillary loss. Tubuloreticular cytoplasmic inclusions are often seen in endothelial cells.

There are myositis specific antibodies and myositis associated antibodies. These antibodies have been helpful in determining subclasses of the inflammatory myositis. The transfer RNA antibodies denote a specific syndrome that consists of interstitial lung disease, a rash called “mechanic’s hands”, arthritis, Raynaud’s phenomenon, and proximal muscle disease. This is also known as the transfer RNA synthetase syndrome. The most important of these antibodies is the anti-Jo 1 antibody that is seen in 20% of cases. This is an auto antibody to the transfer RNA for histidine. The signal recognition particle antibody (anti-SRP) is associated with rapidly progressive proximal muscle disease and cardiac. The anti Mi-2 antibody is found in classic dermatomyositis. There are other antibodies that are myositis associated such as the U1 RNA antibody that is seen in mixed connective tissue disease. The anti-PM SCL antibody is seen in an overlap of polymyositis with scleroderma. A new antibody called the anti-P155/140 (Anti-TIF1g= transcriptional intermediary factor 1-g) is associated with malignancy in
dermatomyositis. This antibody has a positive predictive value of 58% and a negative predictive value of 95% for malignancy associated with dermatomyositis. This has been particularly useful in diagnosing cancer associated myositis (CAM). Cancer is associated with both polymyositis and dermatomyositis although the relative risk is higher with dermatomyositis.

Another subclass *amyopathic dermatomyositis* (ADM) was first coined in 1979 to describe a rare skin disease that has the same cutaneous symptoms as classic dermatomyositis but lacks objective evidence of myopathy. ADM was not fully recognized as a distinct subset of dermatomyositis until the early 1990s. Initially thought to carry a favorable prognosis, ADM may in fact be linked with an increased risk of internal malignancy. Several studies also have indicated an increased risk of lung disease, but the extent of this risk is unclear. It has been estimated that ADM represents about 10% of all cases of dermatomyositis; this percentage may be higher in Asian populations. It is associated with a rare autoantibody, anti-CADM-140 autoantibodies.

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Nature of target antigens</th>
<th>Frequency (%)</th>
<th>Clinical significance</th>
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<tbody>
<tr>
<td><strong>Myositis-specific autoantibodies</strong></td>
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<tr>
<td>Anti-ARS</td>
<td>Histidyl-tRNA synthetase</td>
<td>15–20</td>
<td>Aminosynthetase syndrome (myositis, ILD, polymyositis, mechanic’s hand, Raynaud’s phenomenon and fever)</td>
</tr>
<tr>
<td>Anti-Jo-1</td>
<td>Histidyl-tRNA synthetase</td>
<td>15–20</td>
<td>Aminosynthetase syndrome (myositis, ILD, polymyositis, mechanic’s hand, Raynaud’s phenomenon and fever)</td>
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<tr>
<td>Anti-PL-7</td>
<td>Threonyl-tRNA synthetase</td>
<td>5–10</td>
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<tr>
<td>Anti-PL-12</td>
<td>Alanine-tRNA synthetase</td>
<td>&lt;5</td>
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<td>Anti-EJ</td>
<td>Glutamyl-tRNA synthetase</td>
<td>5–10</td>
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<tr>
<td>Anti-OJ</td>
<td>Isoleucyl-tRNA synthetase</td>
<td>&lt;5</td>
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<td>Anti-KS</td>
<td>Asparaginyl-tRNA synthetase</td>
<td>&lt;5</td>
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<tr>
<td>Anti-Zo</td>
<td>Phenylylalanine-tRNA synthetase</td>
<td>&lt;1</td>
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<tr>
<td>Anti-YRS</td>
<td>Tyrosyl-tRNA synthetase</td>
<td>&lt;1</td>
<td></td>
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<tr>
<td>Anti-SRP</td>
<td>Signal recognition particle</td>
<td>5–10</td>
<td>Necrotizing myopathy</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>218/240 kDa helicase family proteins, components of nucleosome remodeling deacetylase</td>
<td>5–10</td>
<td>DM</td>
</tr>
<tr>
<td>Anti-CADM-140</td>
<td>Interferon induced with helicase C domain protein 1</td>
<td>20–35 in DM (50–70 in C-ADM)</td>
<td>Specific in C-ADM</td>
</tr>
<tr>
<td>Anti-p155/140</td>
<td>Transcriptional intermediary factor 1-γ</td>
<td>15–20 in DM</td>
<td>DM, especially in malignancy-associated DM</td>
</tr>
<tr>
<td>Anti-NXP2 (anti-Mi-2)</td>
<td>NXP2</td>
<td>&lt;5</td>
<td>Juvenile DM (calcinosis and muscle contractures)</td>
</tr>
<tr>
<td>Anti-SAE</td>
<td>SAE</td>
<td>&lt;1</td>
<td>DM</td>
</tr>
<tr>
<td>Anti-200/100</td>
<td>Unknown 200/100 kDa proteins</td>
<td>7 (42 in necrotizing myopathy)</td>
<td>Necrotizing myopathy</td>
</tr>
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<tr>
<th>Myositis-associated autoantibodies</th>
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<tbody>
<tr>
<td>Anti-U1RNP</td>
<td>U1 small nuclear RNP</td>
<td>10</td>
<td>MCTD, overlap syndrome</td>
</tr>
<tr>
<td>Anti-Ro/SSA</td>
<td>52 kDa and 60 kDa protein</td>
<td>13–37 (anti-Ro52) ; 4 (anti-Ro60)</td>
<td>Associated with anti-ARS</td>
</tr>
<tr>
<td>Anti-Ku</td>
<td>70/80 kDa DNA-PK regulatory subunit</td>
<td>20–30</td>
<td>PM–SSc overlap in Japanese</td>
</tr>
<tr>
<td>Anti-Pm-Scl</td>
<td>Nucleolar protein complex of 11–16 proteins</td>
<td>8–10</td>
<td>PM–SSc overlap in Caucasians</td>
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**Clinical symptoms**—The clinical symptoms of inflammatory myositis are proximal muscle pain or myalgia and weakness with weakness in the neck flexors. Additionally the patient may complain of dysphagia because the upper two thirds of the esophagus is striated muscle. If the lung is involved, the patient will complain of dyspnea. Some patients also have a characteristic voice that sounds very nasal. Swallowing is difficult and they may regurgitate through the nose:
fluids are more difficult to swallow than solids.

**Workup**-The workup consists of ordering creatine phosphokinase (CPK), aldolase, liver function tests (because they are elevated with muscle necrosis) and myositis specific and associated antibodies. Of the liver function tests, LDH is more sensitive to muscle necrosis. There is a characteristic EMG that shows a myositis pattern with increased insertional activity, positive sharp waves, and low amplitude. The EMG can help distinguish between myositis, myopathy and neuropathy. MRI has been found to be particularly useful in denoting muscle inflammation from atrophy. There are also characteristic changes in proximal muscle ultrasound. Plain x-rays can reveal cutaneous or muscle calcifications. Computerized tomography may be necessary to evaluate the interstitial lung disease in these patients. Urinalysis and urine myoglobin need to be assessed as massive muscle necrosis may result in renal failure from rhabdomyolysis. Muscle biopsy is characteristic. Other tests may include the following: pulmonary function studies, electrocardiography (ECG), esophageal manometry (in selected patients) or barium swallow.

**Differential diagnoses**-There are other causes for myositis such as virus or bacteria, myotoxins such as alcohol and cocaine, muscular dystrophy, electrolyte disturbances, endocrine disorders such as hypothyroidism or Cushing's disease, and medications such as colchicine, hydroxychloroquine and Statins. Fenofibrates also can cause muscle necrosis but rarely. Myositis is also associated with other connective tissue diseases such as lupus or scleroderma and unexplained myositis can be a sign of systemic Vasculitis.

**Diagnostic clues**-Some diagnostic clues lead you away from the diagnosis of inflammatory myositis are weakness that is episodic or related to activity or fasting; this is seen in myasthenia gravis or metabolic myopathies. Asymmetric or unilateral weakness suggests a neurologic disorder. Facial or ocular weakness rarely occurs in inflammatory myositis and suggests myasthenia gravis or metabolic myopathies. Early muscle atrophy or hypertrophy should suggest a dystrophy. Fasciculation or cramping is rare in inflammatory myositis. There is usually a family history of autoimmune disease in inflammatory myositis. A family history of muscle disorders, however, may suggest a dystrophy. Do not think of inflammatory myositis if there is no fever or rash or arthritis or other connective tissue disease symptoms especially if there are no capillary nail changes. Surprisingly the extremes of the muscle enzymes; that is, <2X or > 100X normal should suggest another diagnosis than inflammatory myositis. If there is no response to therapy or the MRI is normal or atrophic the diagnosis is less likely to be polymyositis or dermatomyositis. Remember that Inclusion Body Muscle Disease is also not responsive to therapy.
The forearm ischemic test is a useful and valuable tool in the diagnosis of metabolic myopathy. Sometimes the muscle enzymes or EMG may fail to make the diagnosis. The muscle enzymes may only be elevated during the episodes of exercise stress. The forearm ischemic test is based upon the fact that exercise will raise both the ammonia and the lactate levels in the blood of the exercise arm in normal controls. If the ammonia rises but the lactate does not, one can suspect a metabolic disorder such as McArdle's disease. McArdle's disease or Glycogen Storage V disease (myophosphorylase deficiency) is usually noticed in childhood, but often not diagnosed until the third or fourth decade of life. Symptoms include exercise intolerance with myalgia, early fatigue, painful cramps, weakness of exercising muscles and myoglobinuria (and possible renal damage or failure). Patients may exhibit a second wind phenomenon in that after 10 min. of rest, the patient may be able to exercise again.

Remember that elderly females are likely to develop hypothyroidism. Hypothyroidism often causes proximal weakness and can cause a significant rise in muscle enzymes. When renal function declines, common drugs may become more toxic. For example, colchicine can become a neuromyotoxin if allowed to accumulate due to renal decline or over dosage. Even in people that have safely taken colchicine for years. Hydroxychloroquine can cause an ocular myopathy in some patients. Antimalarial neuromyopathy is thought to be due to the accumulation of chloroquine or hydroxychloroquine in lysosomes and the subsequent inhibition of lysosomal enzymes in myocyte function.

Cocaine is a myotoxin and in addition to muscle necrosis can cause cardiac muscle damage. Cocaine use is now the most common cause of illicit drug-induced medical problems in the United States, including muscle disease. In one report, at least five percent of cocaine users presenting to one emergency department had evidence of muscle injury based upon CK elevation. Muscle injury can occur after oral or intranasal cocaine use, but may be more common after intravenous use or after smoking the alkaloid free base (crack cocaine) because of the more rapid and higher blood levels of the drug achieved via those routes. Muscle injury can occur after a one time use of the drug or after repeated use. The onset of muscle involvement is usually within hours after drug administration.

Statins, a special case- People at an increased risk for statin induced myopathy include those with prior history of muscle pain with cholesterol-lowering drugs, unexplained cramps or an increase in creatine kinase levels (creatine kinase is an enzyme released in the blood when a muscle is damaged). Drugs like simvastatin and atorvastatin are more likely to cause myopathy. In a small retrospective study of 45 patients, the mean duration of statin therapy before onset of symptoms was 6.3 months (range 1 week to 4 years). In this study the mean duration of myalgia after stopping statin therapy was 2.3 months (range 1 week to 4 months). Muscle symptoms that develop in a patient who has been taking statins for several years are unlikely to have been caused by these drugs. There is a newly necrotizing myopathy has been described with statin use. This entity has a specific muscle biopsy in that there is no inflammatory infiltrate but there is muscle necrosis. This entity is rapidly progressive and requires immunosuppression as well as stopping the statin.

Dilemma – the search for cancer- An important question among rheumatologists is how much
work up needs to be done to look for associated cancer in dermatomyositis or polymyositis. Some
rheumatologists perform only the conventional workup while others do a more extensive look for
cancer including computerized tomography tumor antigens and bone marrow biopsy. A recent
study showed that the more extensive workup could be performed by doing a PET scan.
Selva-O’Callaghan et al found that PET scanning was equal to all of the other tests and imaging
combined.

Goals of Therapy-This is a summary of the treatment for polymyositis and dermatomyositis that
was only briefly mentioned in the presentation. The goals of therapy in polymyositis and
dermatomyositis are to reduce muscle inflammation, decrease weakness, decrease pain, increase
endurance and prevent muscle atrophy. There are few randomized controlled trials (RCT) in
treatment because these diseases are so rare. Choices are largely “eminence-based” not
“evidence-based.” Supportive care such as physical therapy is encouraged; it is also
recommended that patients avoid the sun. Therapy should be individualized. When considering
therapy, duration of the disease, disease activity versus damage, response to prior therapy, and
potential contraindications such as pregnancy or other medications should govern the choice of
treatment. The patient should be evaluated for his comorbid illnesses, rash distribution and
severity, muscle disease, calcinosis, arthritis, interstitial lung disease, and any overlap with other
connective tissue diseases and associated malignancies. The International Myositis Assessment
and Clinical studies group (IMAC) has been formed to devise RCT’s and define improvement in
polymyositis and dermatomyositis.

Medications-Corticosteroids remain the mainstay of initial therapy and is the only FDA
approved drug for dermatomyositis. There is no consensus about the starting dose, oral vs. IV
route of administration or the tapering schedule. Most start at 1 mg per kilogram and continue
that dose for 48 weeks until muscle enzymes normalized. Then the doses lowered by 20 to 25%
of the starting dose monthly until 5 to 10 mg per day is reached. It usually takes about six months
then the maintenance dose of 5 to 10 mg per day is continued for an additional six months or until
active disease is completely suppressed. Hydroxychloroquine is not useful with the skin disease
dermatomyositis, although it may be used with the arthritis associated with these diseases.

Methotrexate has been used for over 40 years in dermatomyositis is helpful to improve muscle
strength and to normalized muscle enzymes. Methotrexate is helpful for skin, muscle, and joint
manifestations. It is controversial whether it can be used in patients with interstitial lung disease.
Methotrexate is contraindicated in pregnancy as it is teratogenic and may decrease
spermatogenesis. It is used orally or subcutaneously with a maximum dose of 25 mg weekly and
use folic acid 1 mg per day to reduce side effects. Methotrexate in a randomized controlled trial
with azathioprine showed no statistical difference in regaining muscle strength. Warn patients
that methotrexate is a photo sensitizer and may interact with Bactrim for PCP prophylaxis or for a
UTI.

Azathioprine is also used for dermatomyositis and polymyositis treatment; it is less effective for
the associated arthritis than methotrexate. It is recommended that you test for Thiopurine
methyltransferase (TPMT), a key enzyme in azathioprine metabolism mediating both
immunosuppression and cytotoxicity. TPMT activity may be influenced by a mutation in the
TPMT gene resulting in individual differences in azathioprine metabolism. Individuals
heterozygous for TPMT mutations or with low TPMT activity may be susceptible to azathioprine toxicity. Leukopenia, increased liver enzymes, and pancreatitis are potential adverse reactions. Azathioprine may be used safely during pregnancy and in interstitial lung disease. Be careful and reduce dose if used with allopurinol. One study has shown that daily azathioprine given with weekly methotrexate increased muscle strength over six months.

Mycophenolate mofetil may be used for the interstitial lung disease but is contraindicated in pregnancy. The does used ranges from 500mg PO twice daily to 1500mg PO twice daily. Mycophenolate mofetil is also used for recalcitrant dermatomyositis related skin disease.

Intravenous immunoglobulin (IVIG) is also used for recalcitrant muscle disease, not helpful for lung involvement. The standard dose is 2 Grams per kilogram given in five or two divided doses per month in an IV infusion. It is important to check the quantitative immunoglobulin’s to rule out IgA deficiency before starting. IVIG is generally given for 3 to 6 months but is rarely employed as a first-line therapy. IVIG is beneficial in refractory muscle disease or flares or rapidly progressive dermatomyositis or polymyositis. It is also useful in patients with lung involvement and esophageal dysmotility. IVIG can also lower the corticosteroid dose required for maintenance and can be safely used in pregnancy. Keep in mind that while 30% of patients do have some type of adverse reaction—whether it is mild or severe—that means that 70% of patients do not experience adverse reactions. Pre-medicating is one way to mitigate tolerability-associated reactions. Rate of administration is important; slow infusion at first and titrate upward as tolerated.

Plasmapheresis is not useful in corticosteroid resistant polymyositis for dermatomyositis. In a randomized controlled clinical trial plasmapheresis was no better than sham apheresis.

Other medications- Cyclophosphamide may be given for severe refractory pulmonary disease. Cyclosporine inhibits T cell proliferation and selectively inhibits T cell mediated responses. Cyclosporine is administered at a dose of 100 to 150mg twice-daily. Side effects include nephrotoxicity, neurotoxicity, disturbances of glucose metabolism, hyperkalemia, headache, tremor, hypertension, and G.I. symptoms.

Tacrolimus is a macrolide immunosuppressant; it binds the lymphocyte that alters the activity of calcineurin and leads to the inhibition of T cell activation and IL-2 transcription. It is mostly used in interstitial lung disease and has been shown to be effective in corticosteroid sparing in anti Jo 1 positive patients with interstitial lung disease.

TNF alpha inhibitors have been shown to steroid spare. Rituximab, a chimeric monoclonal antibody directed against CD20 on B cells, has also been shown to be useful in adult and pediatric polymyositis and dermatomyositis patients. Reported as an abstract at the ACR scientific meeting in 2010, it was shown that 83% of the IIM patients met the definition of improvement but the primary and secondary endpoints were not met.
References:


