# Neuromuscular Conference

# Inflammatory Myopathy

Dr. Hemang Shah

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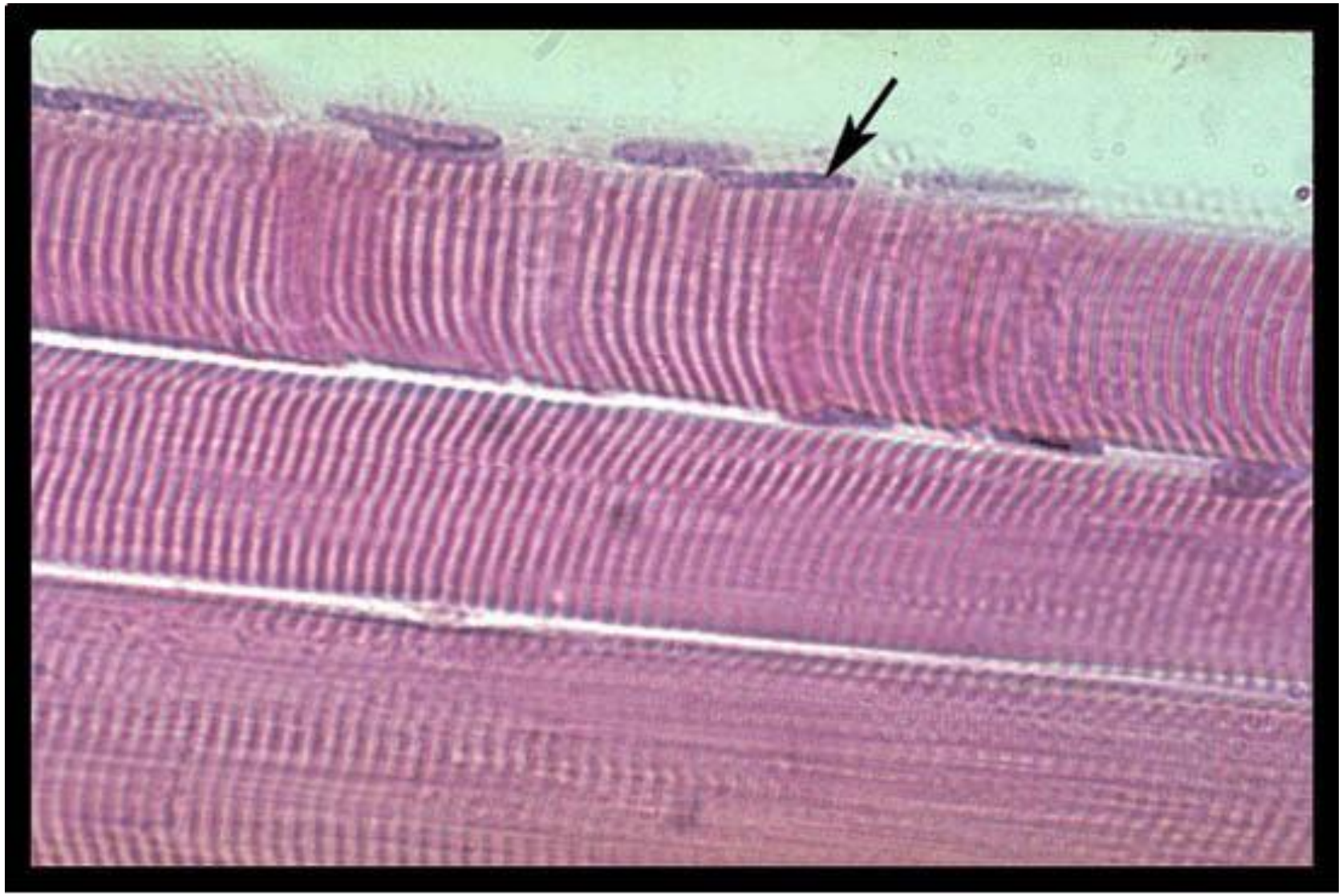
# Outline

Muscle
Anatomy
Physiology
Pathology
Clinical Presentation
Management

# Skeletal Muscle



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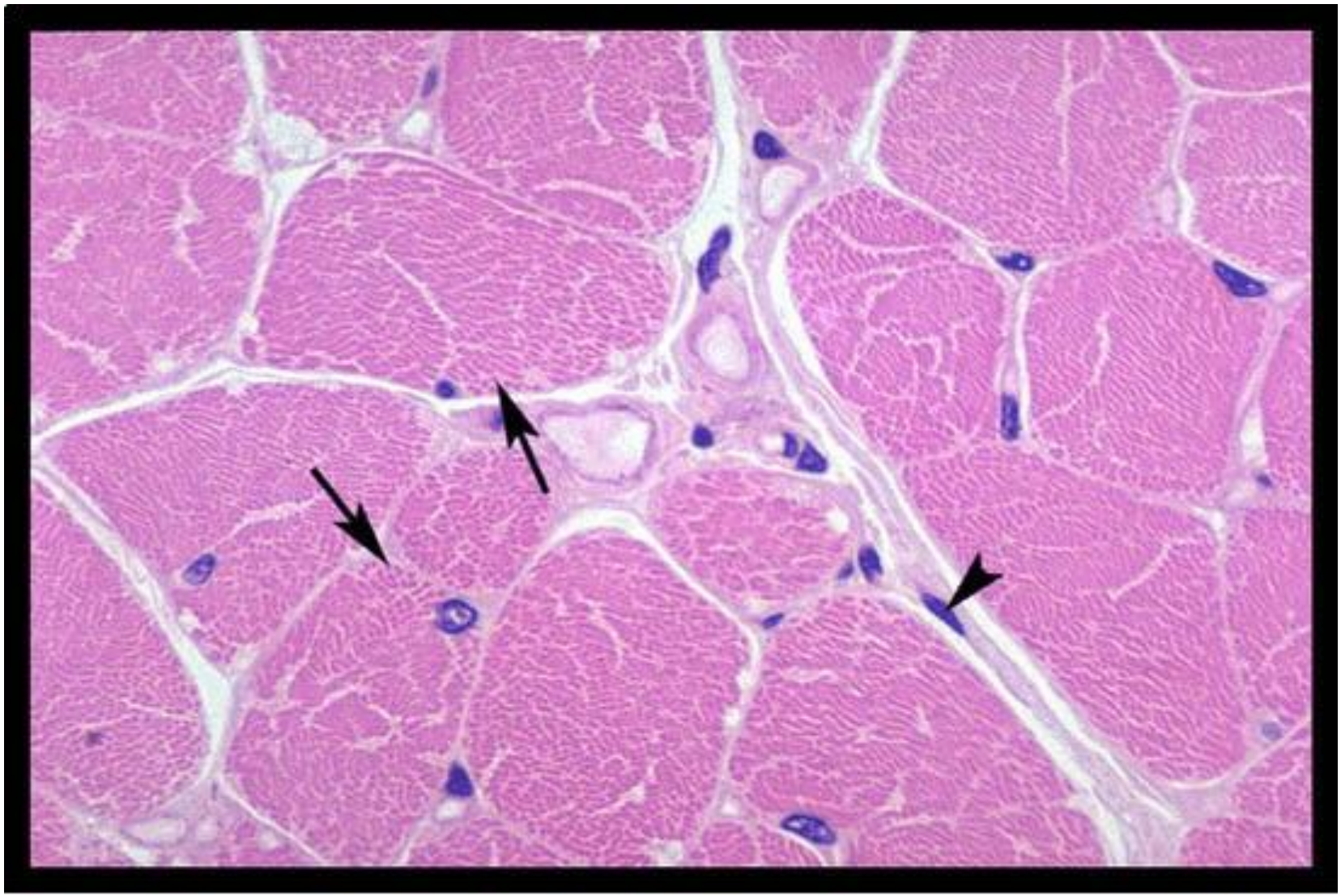
# Connective Tissue



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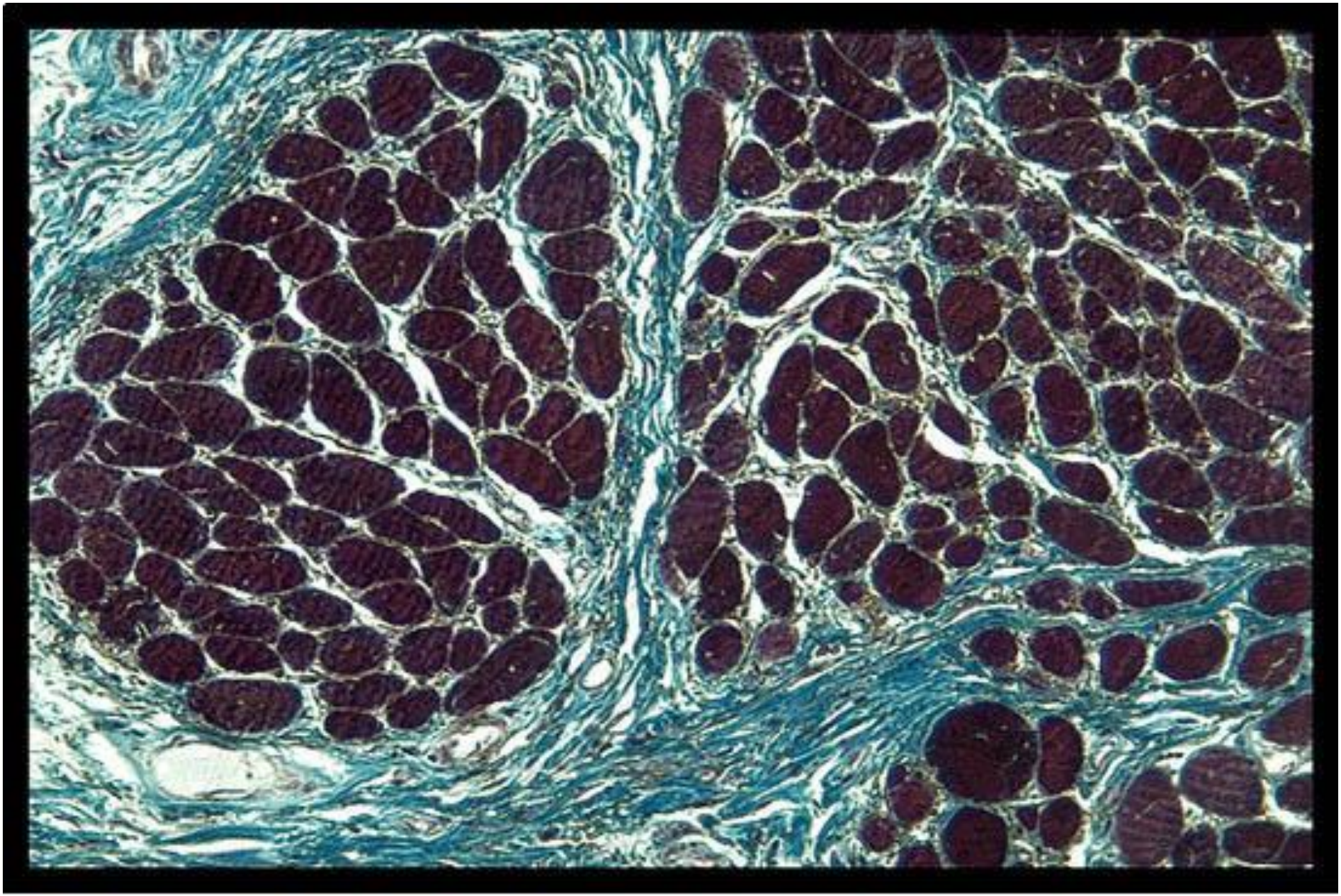

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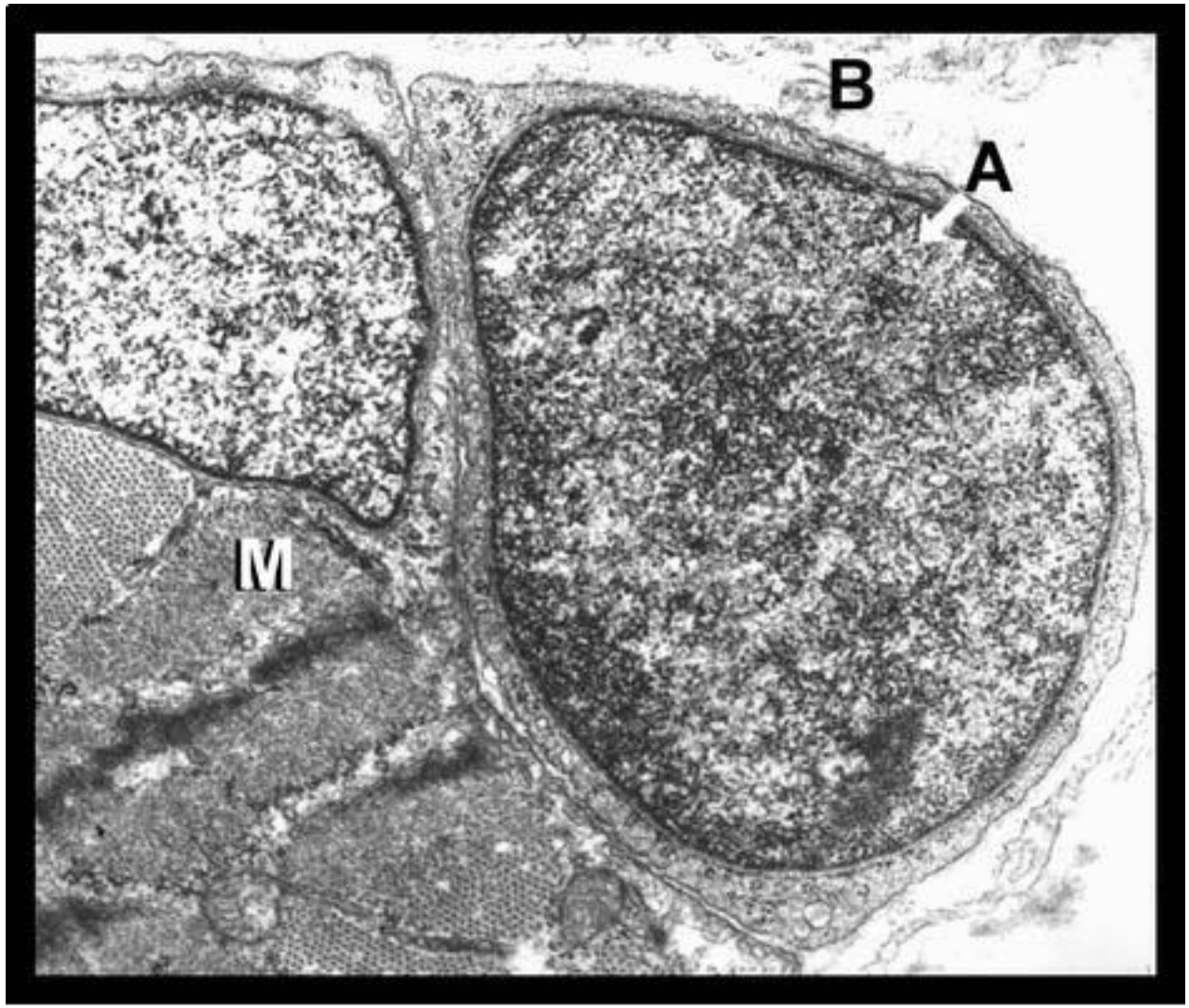
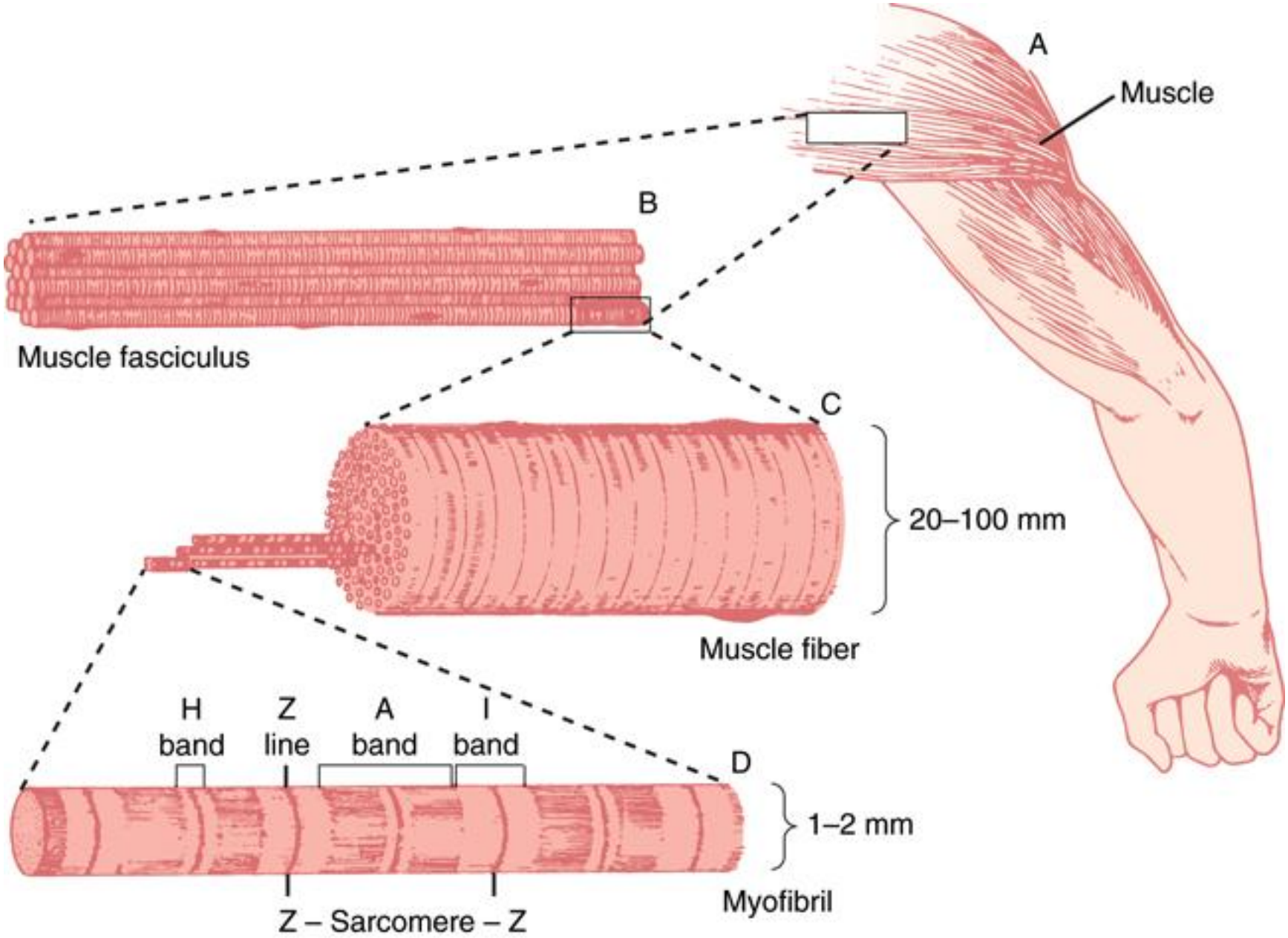
# Electron Microscopy






**Micrograph courtesy of Edward Schultz, University of Wisconsin**

# Sarcomere

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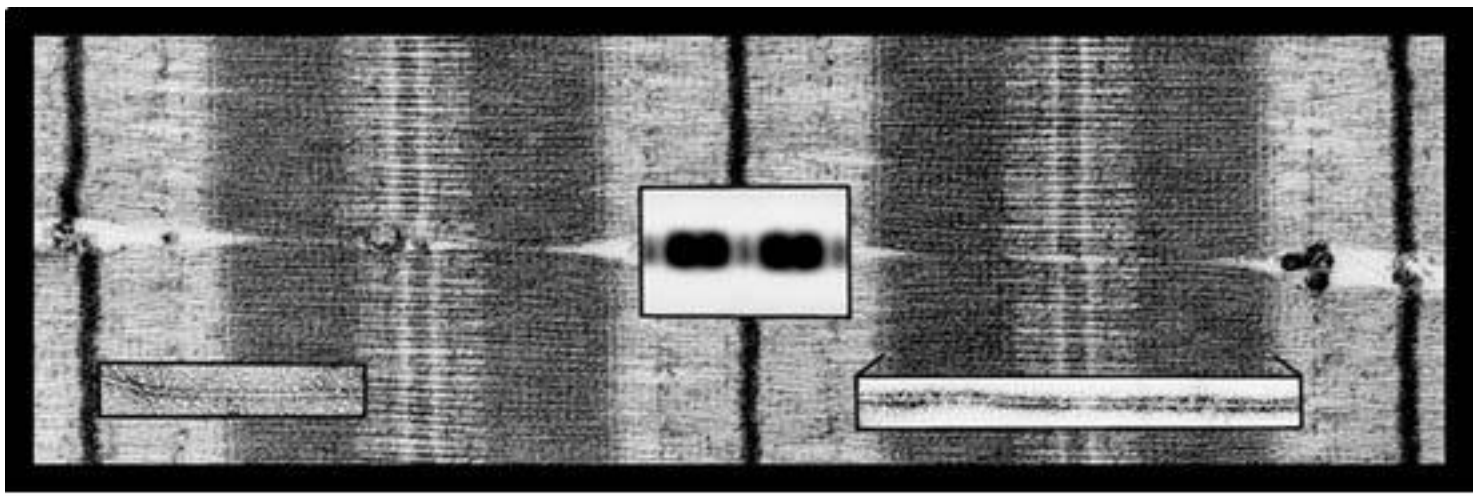

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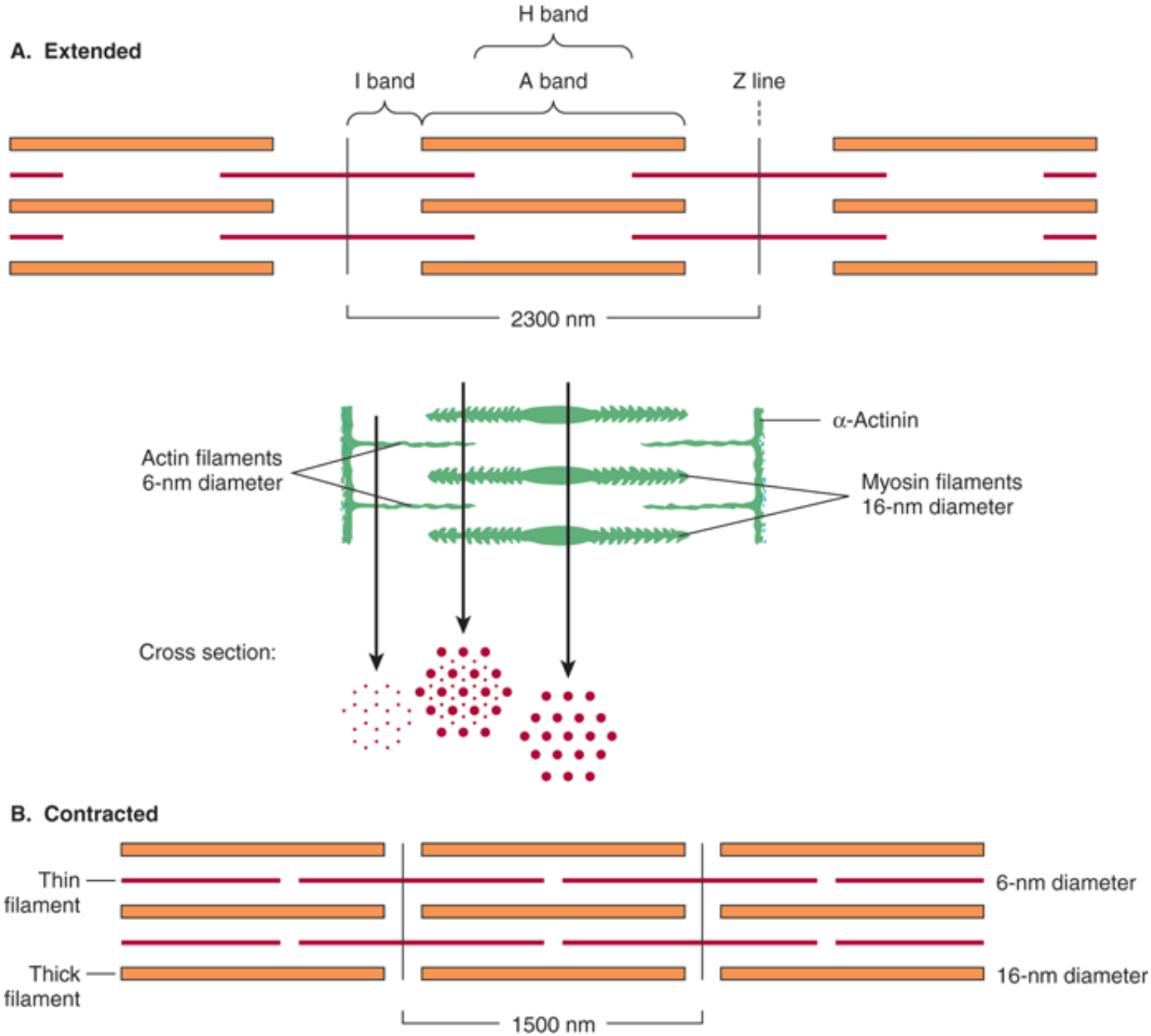


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# Actin Myosin dance

http://www.youtube.com/watch?v=EdHzKYDxrKc&feature=related

http://www.youtube.com/watch?v=VQ4OMSi6qAg

# Approach to the pt. with muscle disease

- different diseases share certain common symptoms and syndromes.
- fatigue, pain, limpness or stiffness, spasm, cramp, twitching, or a muscle mass or change in muscle volume
- weakness is by far the most frequent and at the same time the most elusive
- fatigability - myasthenia gravis - chronic systemic disease or with asthenic anxiety or depression
- attempt to conduct the examination under circumstances that duplicate the complaints
-

# Physical/Strength testing

- cooperation
- give away
- pain
- Watch: waddling gait, protruberant belly, lordosis
- touch it
- tap it (percussion myotonia - myotonia congenita, paramyotonia congenita, myotonic dystrophy, myoedema - myxoedema,

# Idiopathic Inflammatory Myopathies

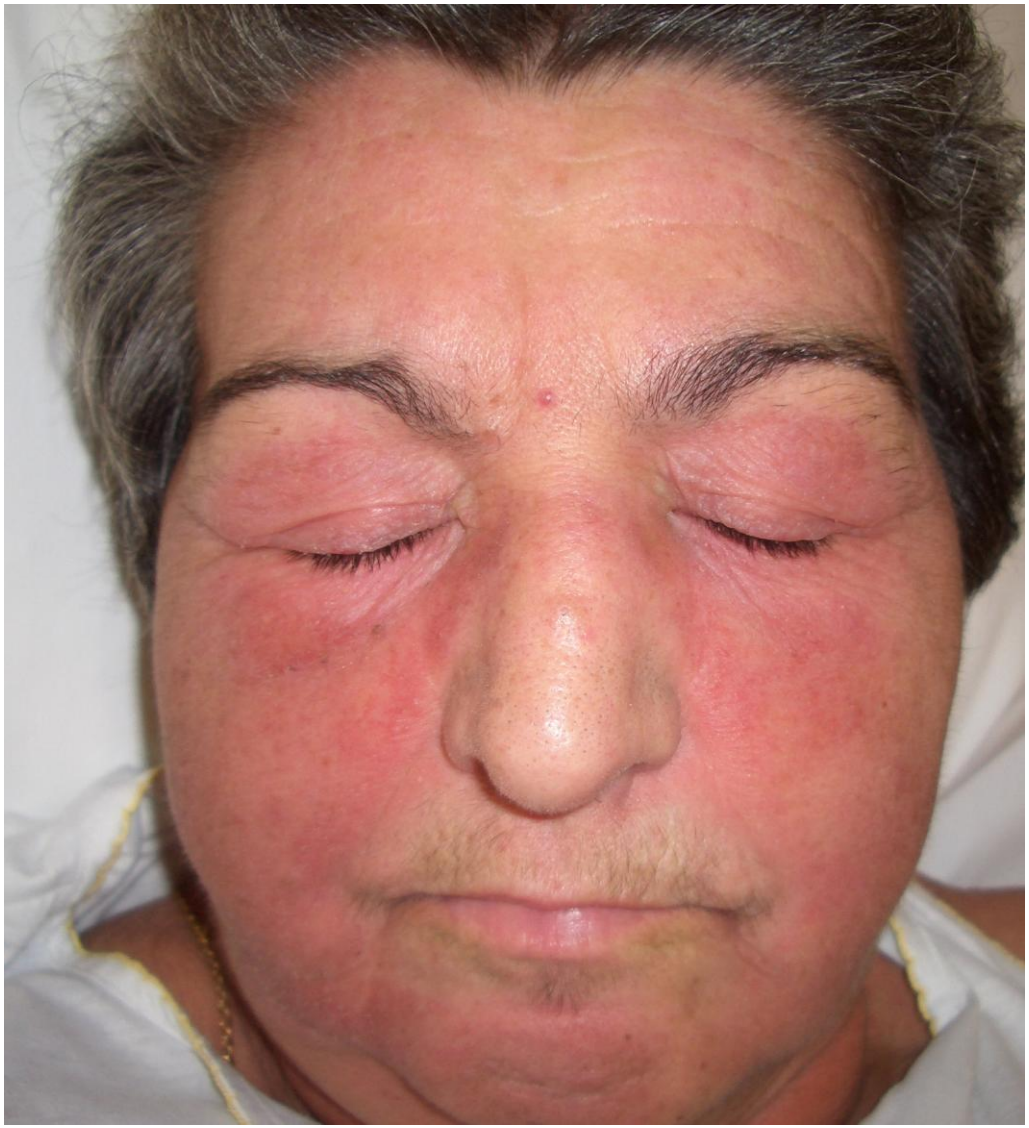
- Dermatomyositis (DM),
- Polymyositis (PM),
- Inclusion body myositis (IBM).

*patient's pattern of weakness is the most important piece of the puzzle.*

# Dermatomyositis

- F>M
- present at any age (5 to 14, adult)
- Onset of weakness is typically subacute (over several weeks),
- The neck flexors, pectoral, and pelvic girdle muscles are the earliest and most severely affected.
- Preceded by fatigue, low-grade fever, and a rash.
- Dysphagia, 30% of patients with DM
- DTR – OK except end stage disease

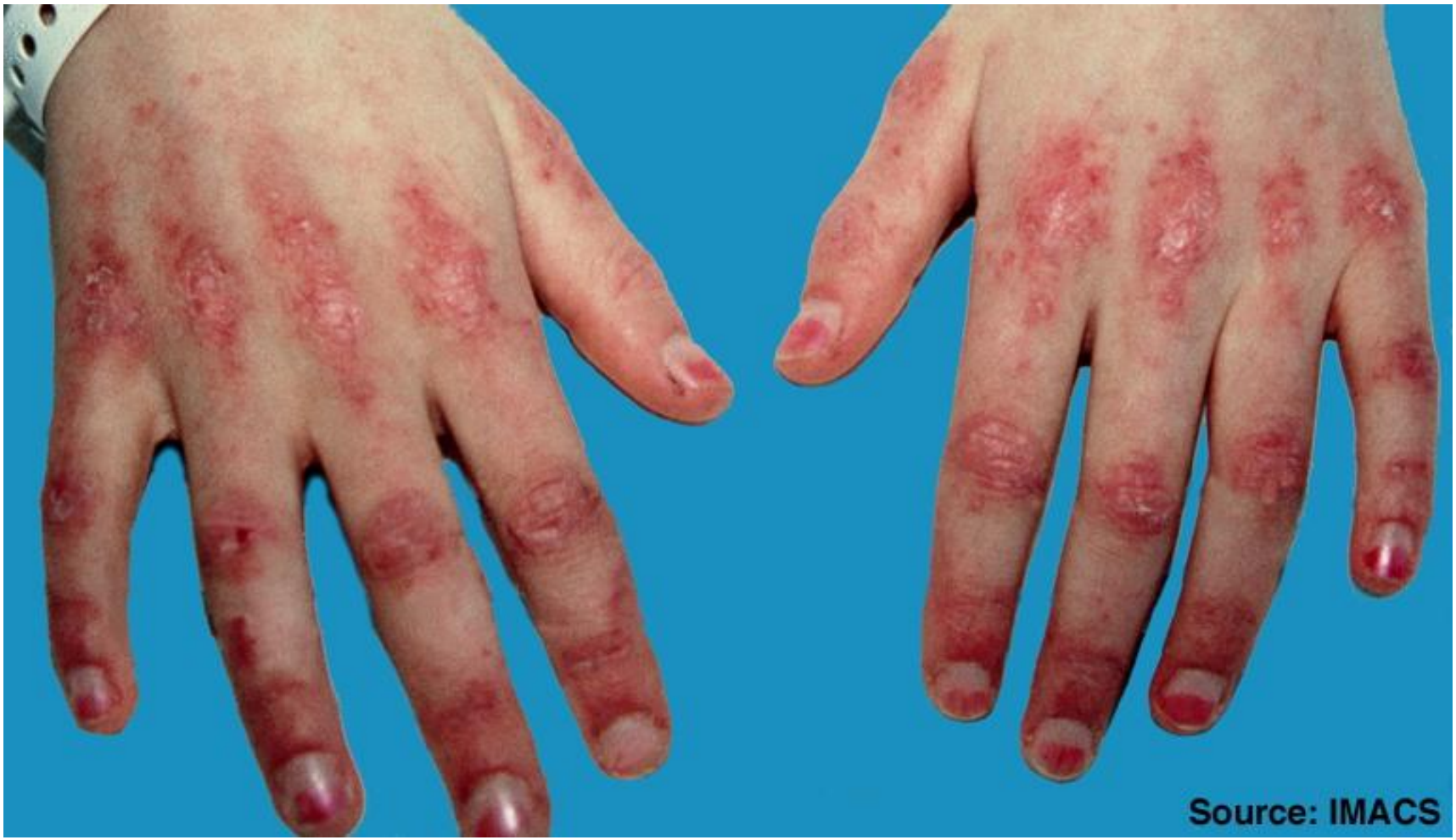
# Rash

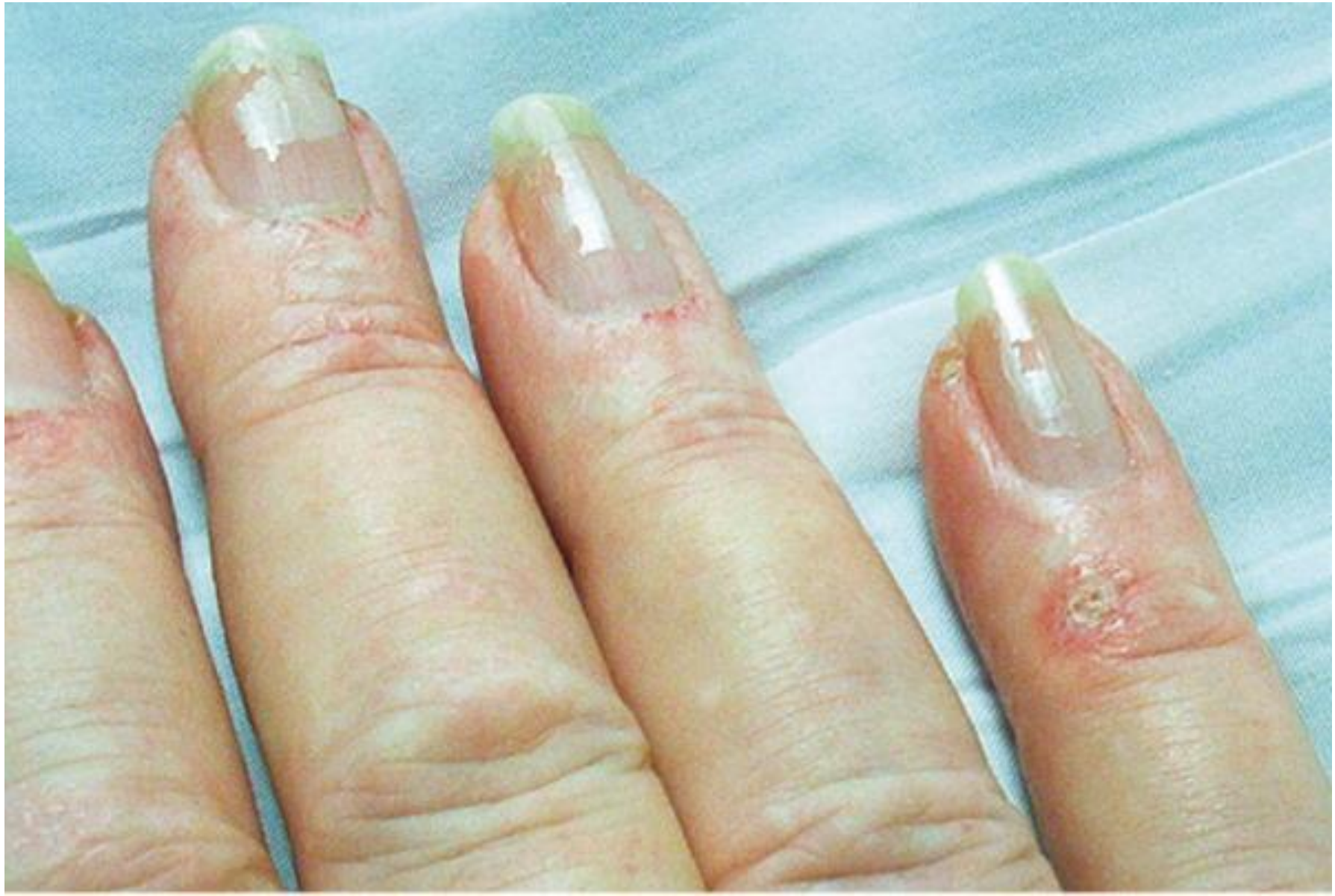


- Accompanies or precedes the onset of muscle weakness
- Heliotrope rash (a purplish discoloration of the eyelids)

From: DermAtlas

- Gottron's papules : papular, erythematous, scaly lesions over the knuckles.





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# Case 1 - History

- 58-year-old woman presents with a 6-week history of progressive muscle aching and weakness involving her arms and legs.
- Symptoms began in the legs with difficulty climbing stairs and arising from chairs. In the last 4 weeks, she has had difficulty lifting her arms over her head.
- She has noticed some redness in her face, neck, and hands with some itchiness over the past couple weeks.
- She has no complaints of numbness or tingling, blurred or double vision, chewing or swallowing difficulties, slurred speech, or dyspnea. She has no complaints of palpitations, chest pain, bowel or bladder problems, blood in the urine or stool, or swollen or tender lymph nodes.
- Her past medical history is otherwise unremarkable, and she is taking no medications. Family history is unremarkable for any neuromuscular or autoimmune disorders.

# Exam

Skin examination reveals moderate to severe erythema involving her face and scalp, nape of the neck, anterior chest, and area around her knuckles (Gottron's sign). Periungual nail bed erythema and telangiectasia of some cuticles are visible  She has some ulceration of her fingers.

Manual muscle testing demonstrates the following :
neck flexion 4-; neck extension 5;
shoulder abduction/elbow flexion/elbow extension 4-,
wrist flexion/extension 4+,
hip flexion/extension/abduction 3-,
knee flexors 4-, knee extensors 4+,
ankle dorsiflexors 4+, and plantar flexors 5.
Sensory examination and muscle stretch reflexes are intact.

# Diagnostic Test

A serum CK is within normal limits at 134 U/L.

ANA is positive at 1:120.

Antibodies directed against extractable nuclear antigens and Jo-1 are absent.

Chest x-ray, electrocardiogram, and pulmonary function tests are normal.

EMG showed myopathic changes

A biceps brachii muscle biopsy shows perivascular inflammation in the perimysium along with perifascicular atrophy.

# Treatment

Diagnosed with dermatomyositis

Started on prednisone 100 mg by mouth daily and switched to 100 mg every other day after 2 weeks.
She is also started on methotrexate 7.5 mg weekly.

A bone density scan (DEXA) shows no osteoporosis. She is given a prescription for alendronate 35 mg weekly as well as calcium and vitamin D for osteoporosis prophylaxis because of the anticipation that she may be on corticosteroids for an indefinite period of time.

A chest, abdominal, and pelvic CT scan and colonoscopy reveal no abnormality. However, mammogram demonstrates a suspicious lesion in the left breast. The lesion is biopsied and is consistent with adenocarcinoma. She undergoes a mastectomy and chemotherapy.

# Happy ending?

She is maintained on prednisone, but the methotrexate is discontinued while she receives the chemotherapy.

She eventually is able to wean off the prednisone after about 18 months, but within 6 months of stopping the prednisone she has an exacerbation of the weakness and rash.

She is restarted on prednisone and methotrexate and improves.

Eventually, she is able to be weaned off prednisone and be maintained on methotrexate.

# Associated Manifestations

Cardiac: arrythmia, pericarditis, myocarditis, CHF
Pulmonary:

Interstitial Lung Disease

* Complicates at least 10% of adult DM (symptoms: dyspnea, nonproductive cough) abruptly or insidiously and often precede
Chest radiographs reveal a diffuse reticulonodular pattern with a predilection for involvement at the lung bases

- In the more fulminant abrupt-onset cases, a diffuse alveolar pattern or "ground-glass" appearance is seen. Pulmonary function tests demonstrate restrictive defects and decreased diffusion capacity, while hypoxemia is evident on arterial blood gasses.
- Antibodies directed against t-histidyl transfer ribonucleic acid (RNA) synthetase, so-called anti-Jo-1, are present in at least 50% of ILD cases associated with inflammatory myopathies.
- Patients with significant oropharyngeal and esophageal weakness can develop aspiration pneumonia.

# Conti...

**Gastrointestinal.** dysphagia and delayed gastric emptying. More common in childhood DM compared with adult DM. The vasculopathy can result in mucosal ulceration, perforation, and life-threatening hemorrhage

**Joints.** Arthralgias with or without arthritis are a frequent presenting feature. Arthritis is typically symmetrical and involves both the large and small joints. The arthralgias and myalgias often ease when the limbs are flexed, which unfortunately leads to the development of flexion contractures across the major joints. Plantar flexion contractures at the ankles leading to toe walking are a common early finding in childhood DM.

**Vasculopathy.** In addition to the skin, muscle, and gastrointestinal system, necrotizing vasculopathy may affect other tissues including the eyes (retina and conjunctiva), kidneys, and lungs.

Rarely, massive muscle necrosis can lead to myoglobinuria and acute renal tubular necrosis.

# Conti...

Malignancy:

* Ranging from 6% to 45%. rare in childhood DM
- Detection of an underlying neoplasm can precede or occur after the diagnosis of DM; the majority of malignancies are identified within 2 years of the presentation of the myositis.
- The risk of malignancy is greater in patients over the age of 40 years.
- The severity of the inflammatory myopathy does not appear to correlate with the presence or absence of a neoplasm. Treatment of the underlying malignancy sometimes results in improvement of muscle strength.

Work up:
A comprehensive history and annual physical examinations with breast and pelvic examinations for women and testicular and prostate examinations for men.
Complete blood count (CBC), routine blood chemistries, urinalysis, and stool specimens for occult blood. Chest and abdominal/pelvic computed tomography (CT) scans and mammogram are routinely ordered, as well as a colonoscopy, for anyone over the age of 50 years or those with gastrointestinal symptoms.

# Diagnostic work up: Labs

Necrosis of muscle fibers results in elevations of serum CK, aldolase, myoglobin, lactate dehydrogenase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

Serum CK is the most sensitive and specific marker for muscle destruction. Serum CK is elevated in more than 90% of patients with DM, and levels can be as high as 50 times the normal value.
However, serum CK levels do not correlate with the severity of weakness and can be normal even in markedly weak individuals, particularly in childhood DM.

Erythrocyte sedimentation rate is usually normal or only mildly elevated and is not a reliable indicator of disease severity.

ANA can be detected in 24% to 60% of patients with DM. These antibodies are much more common in patients with overlap syndromes

# Diagnostic work up: Labs

Myositis-specific antibodies (MSAs) – causative?, epiphenomenon

The MSAs include:

(1) the cytoplasmic antibodies directed against translational proteins (ie, various tRNA synthetases and the antisignal recognition particle) and

(2) Against Mi-2 and Mas antigens. The most common of the antisynthetases is the anti-Jo 1 antibody, which is associated with ILD and arthritis and is demonstrated in up to 20% of patients with inflammatory myopathy.

The presence of these anti-Jo-1 antibodies has been associated with only a moderate response to treatment and a poor long-term prognosis.

(3) Mi-2 antibodies are seen almost exclusively in DM and can be found in 15% to 20% of patients with DM. The anti-Mi-2 antibodies are associated with acute onset, florid rash, good response to therapy, and favorable prognosis.

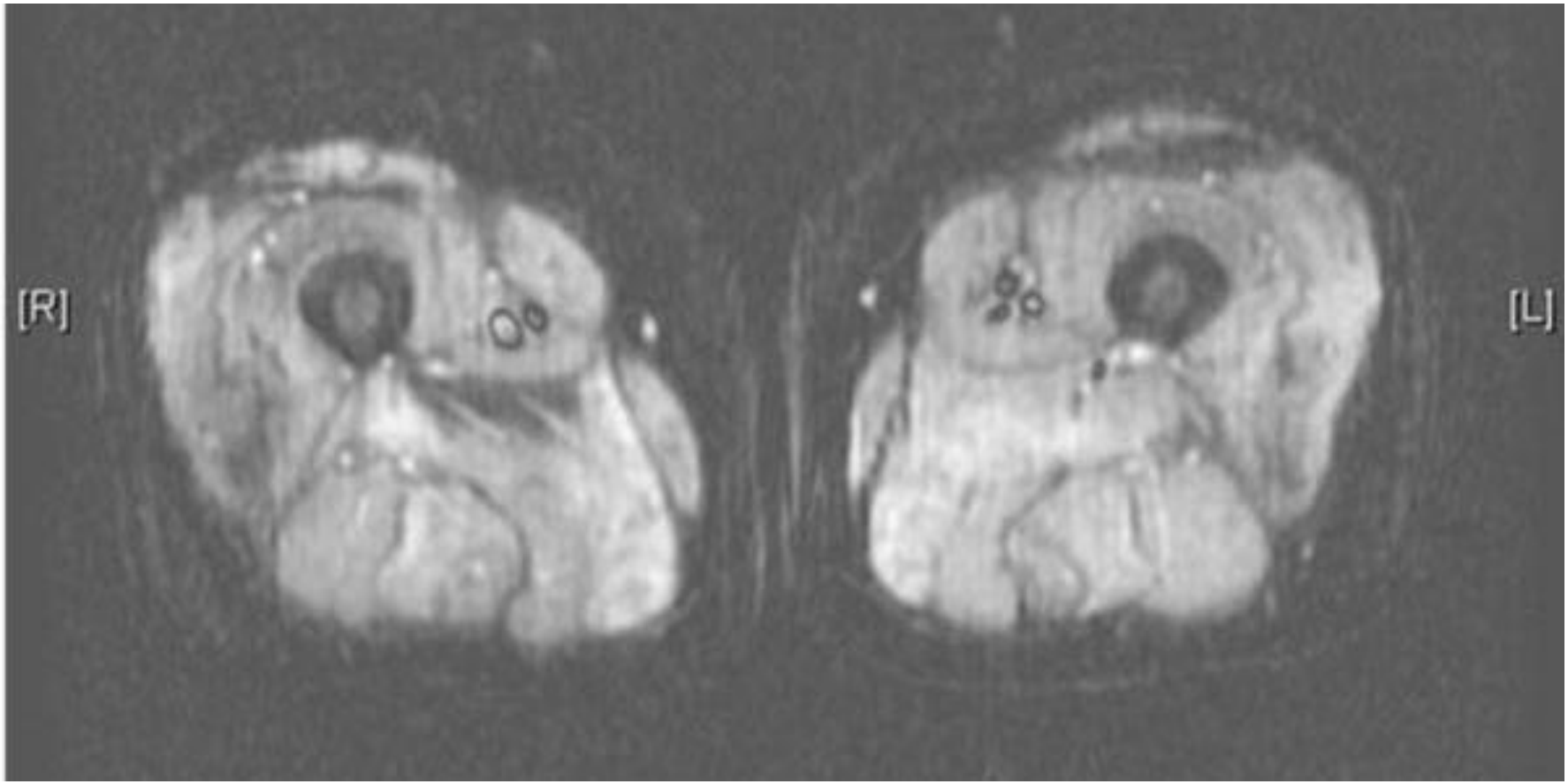
# Diagnostic work up: EMG

(1) Increased insertional and spontaneous activity with fibrillation potentials, positive sharp waves, and occasionally pseudomyotonic and complex repetitive discharges;
(2) Small-duration, low-amplitude, polyphasic motor unit action potentials (MUAPs)
(3) MUAPs that recruit early but at normal frequencies.
(4) Advance disease: recruitment may be decreased (fast-firing MUAPs) due to the loss of muscle fibers of entire motor units. insertional activity may be decreased secondary to fibrosis.
(5) In addition, large-duration polyphasic MUAPs may also be seen later in the course, reflecting chronicity of the disease with muscle fiber splitting and regeneration rather than a superimposed neurogenic process.
(6) The amount of spontaneous EMG activity is reflective on ongoing disease activity.

# Uses of EMG

(1) EMG can be helpful in determining which muscle to biopsy in patients with only mild weakness.
(2) Previously responsive myositis patients who become weaker by differentiating worsening strength from increased disease activity from weakness secondary to type 2 muscle fiber atrophy from disuse or chronic steroid administration. Isolated type 2 muscle fiber atrophy is not associated with abnormal spontaneous activity on EMG.

# Diagnostic work up: Radiology

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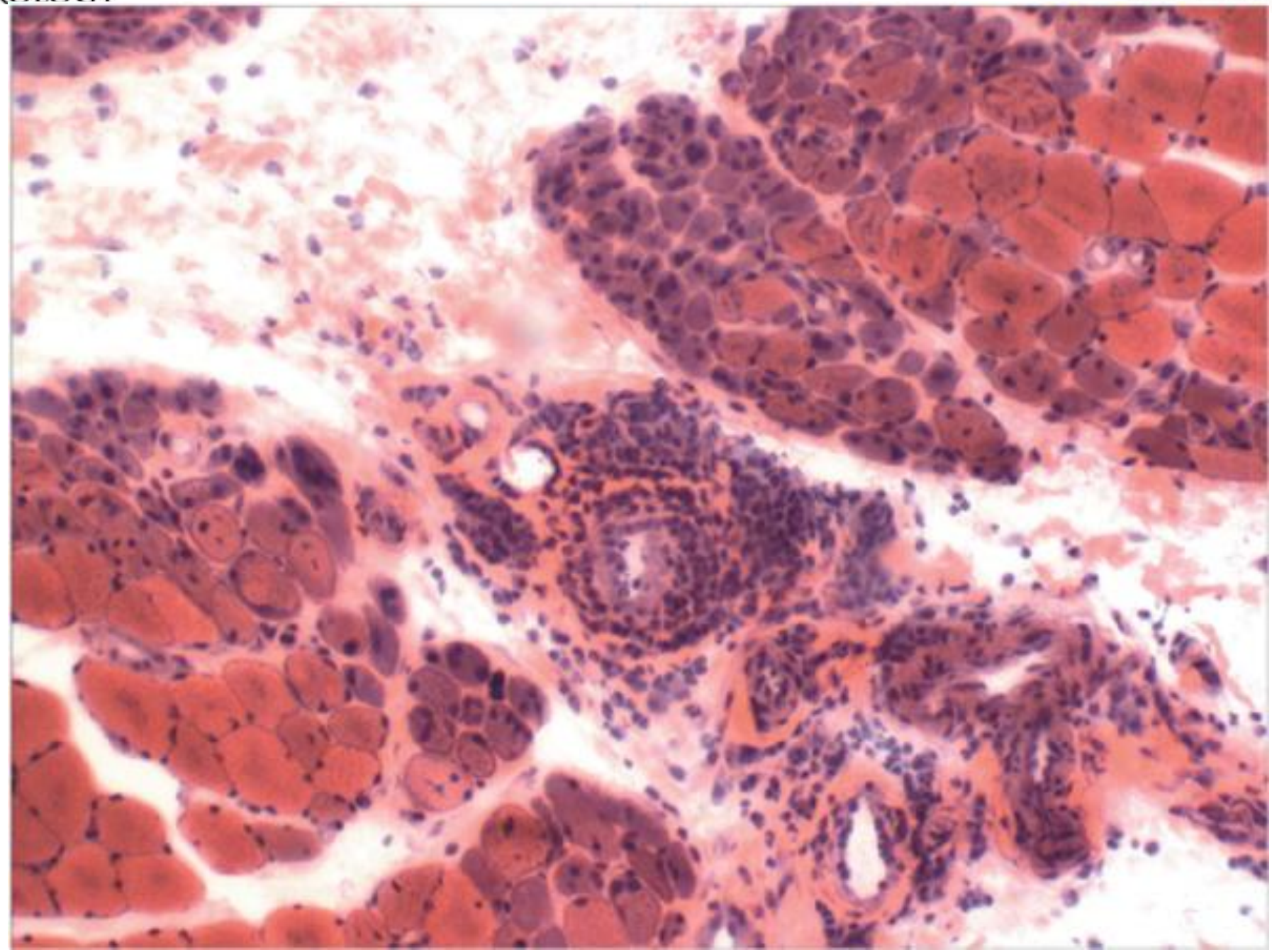
# Diagnostic work up: Pathology



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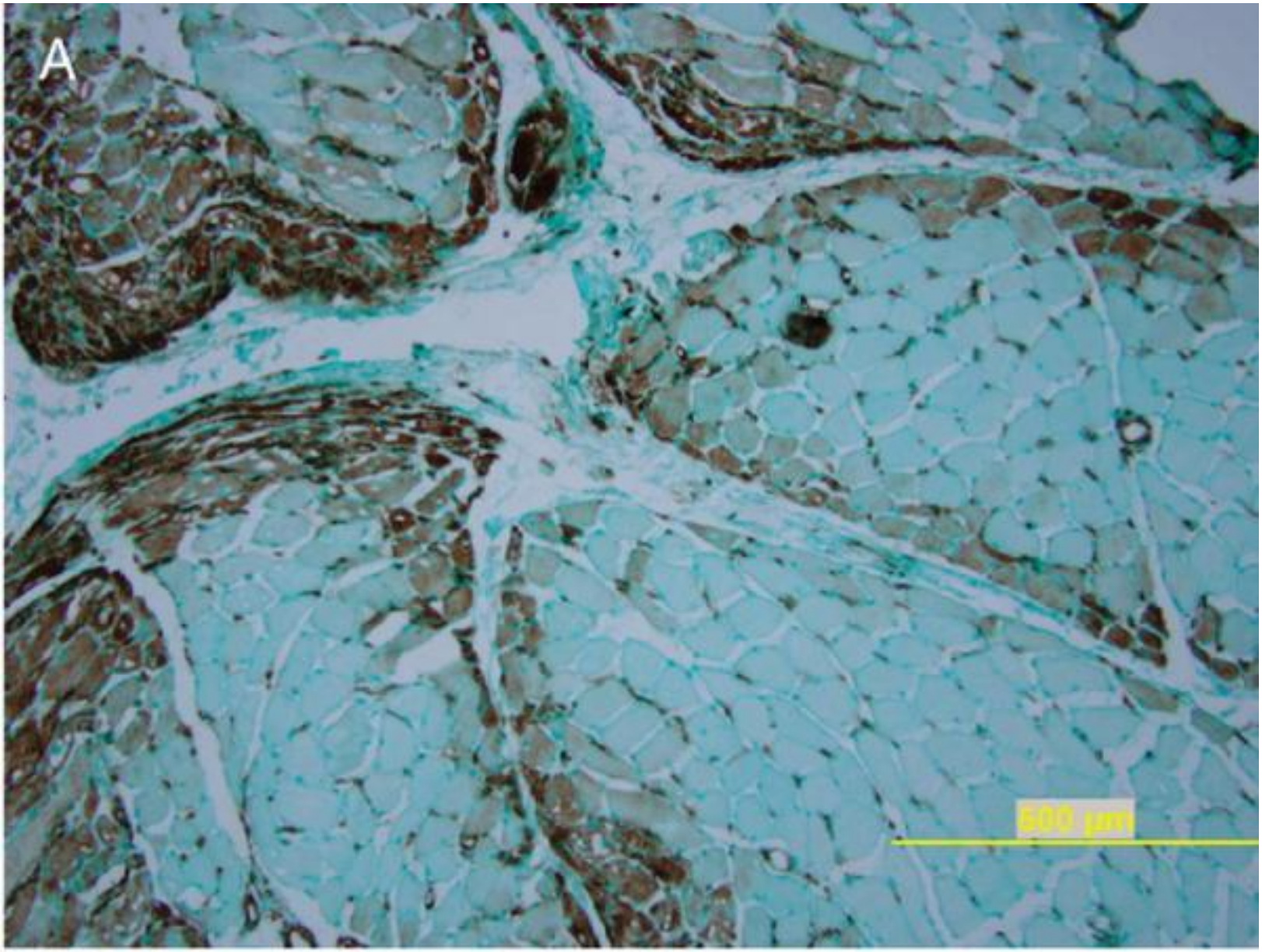
# Pathogenesis

- humorally mediated microangiopathy
- ischemic damage and occasionally infarction of muscle fibers. perifascicular atrophy is the result of hypoperfusion to the watershed region of muscle fascicles

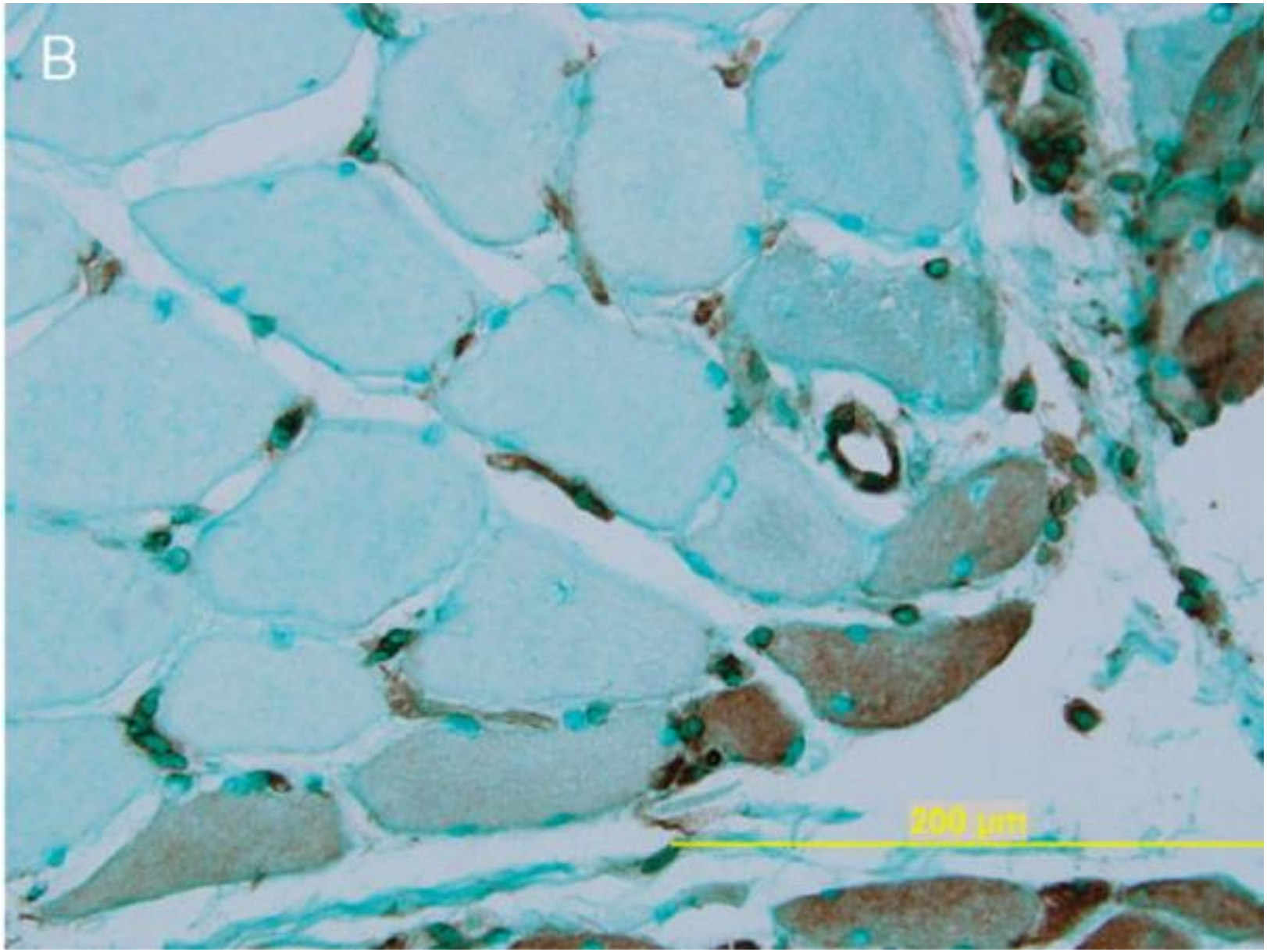
# Do we really know what is going on?

- It has never been demonstrated that the perifascicular region is indeed the watershed area in muscle fibers or that the perifascicular fibers are more prone to ischemic damage.
- Perifascicular atrophy is not evident in ischemic muscle damaged from vasculitis.
- Perifascicular atrophy has not been demonstrated in animal models of small vessel ischemia. On the contrary, such models demonstrate a predilection for the involvement of more centrofascicular fibers.

**Greenberg SA, Amato AA. Uncertainties in the pathogenesis of adult dermatomyositis. Curr Op Neurol 2004;17:359-364.**




Immunohistochemistry of muscle biopsy in a patient with dermatomyositis reveals MxA staining of perifascicular muscle fibers (*A*) and of small blood vessels (*B*).

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# Prognosis

- In the absence of malignancy, prognosis is favorable in patients with DM.
- Poor prognostic features are increased age, associated ILD, cardiac disease, and late or previous inadequate treatment. Five-year survival rates of adult DM range from 70% to 93%.
- The mortality rate in children is very low.

# INCLUSION BODY MYOSITIS

- insidious onset of slowly progressive proximal and distal weakness that generally develops after the age of 50 years
- delay in diagnosis, averaging approximately 6 years
- M>F
- Early asymmetrical weakness and atrophy of the quadriceps, volar forearm muscles (ie, wrist and finger flexors), and the ankle dorsiflexors

# Case 2 - History

- A 74-year-old woman complains of difficulty climbing stairs for approximately the past 5 years. Prior to this time, she had been very active and played tennis regularly with her sister. She feels that the lower extremity weakness has been very slowly progressive, and she now has to hold onto a rail when going up the stairs and has difficulty getting off low seats without using the arm rest. She denies any weakness in her upper extremities. She has had no problems opening cans, using keys, or unscrewing jars. She denies any history of dysphagia or respiratory difficulties. There is no history of diplopia or other visual symptoms. She denies any pain associated with this weakness. There is no history of sensory loss or paresthesias
- Past medical history is unremarkable. Her only medication is lisinopril. There is no family history of any neuromuscular disease.

# Exam

- Physical examination reveals very mild orbicularis oris weakness of 4+/5. Neck flexor strength is 4/5. Neck extensors are 5/5. Deltoid strength is also 5/5 bilaterally. Strength is 4+/5 in the biceps bilaterally, and 4-/5 in the triceps, also bilaterally. Wrist extensors are 5/5. Wrist flexors, finger extensors, and superficial finger flexors are 4/5 bilaterally (perhaps slightly weaker on the left). Deep finger flexors are 3+/5 bilaterally (again perhaps slightly weaker on the left). In the lower extremities, hip flexion is 4/5 bilaterally. Quadriceps strength is 4-/5 bilaterally. Hamstring strength is also 4+/5 bilaterally. Dorsiflexion is 4/5 bilaterally, and plantar flexion is 5/5 bilaterally. There is mild reduction in vibratory perception in the toes. Deep tendon reflexes are normal in the arms but absent at the knees and ankles. Gait is wide based, and she has a tendency to look her knees when she walks. She also has a steppage quality and lands flat-footed.

# Labs

- Her serum CK level is elevated at 545 U/L. Other laboratory tests, including CBC, basic metabolic profile, thyroid function tests, ANA, erythrocyte sedimentation rate, and a serum protein electrophoresis, are normal. Nerve conduction studies are normal except for absent sural sensory nerve action potentials, which could be normal for age. The EMG demonstrates fibrillation potentials and positive sharp waves in proximal and distal arm and leg muscles and thoracic paraspinals along with a mixture of large and small polyphasic MUAPs. No fasciculation potentials or myotonic discharges are present. Recruitment of MUAPs is early. A muscle biopsy shows variability in muscle fiber size, small groups of atrophic muscle fibers, many fibers with rimmed vacuoles, and endomysial inflammatory cell infiltrate with invasion of nonnecrotic muscle fibers. Abnormal congophilic inclusions are evident in vacuolated fibers. Electron microscopy 15-nm to 18-nm tubulofilamentous inclusions are appreciated in the cytoplasm.

# Now what?

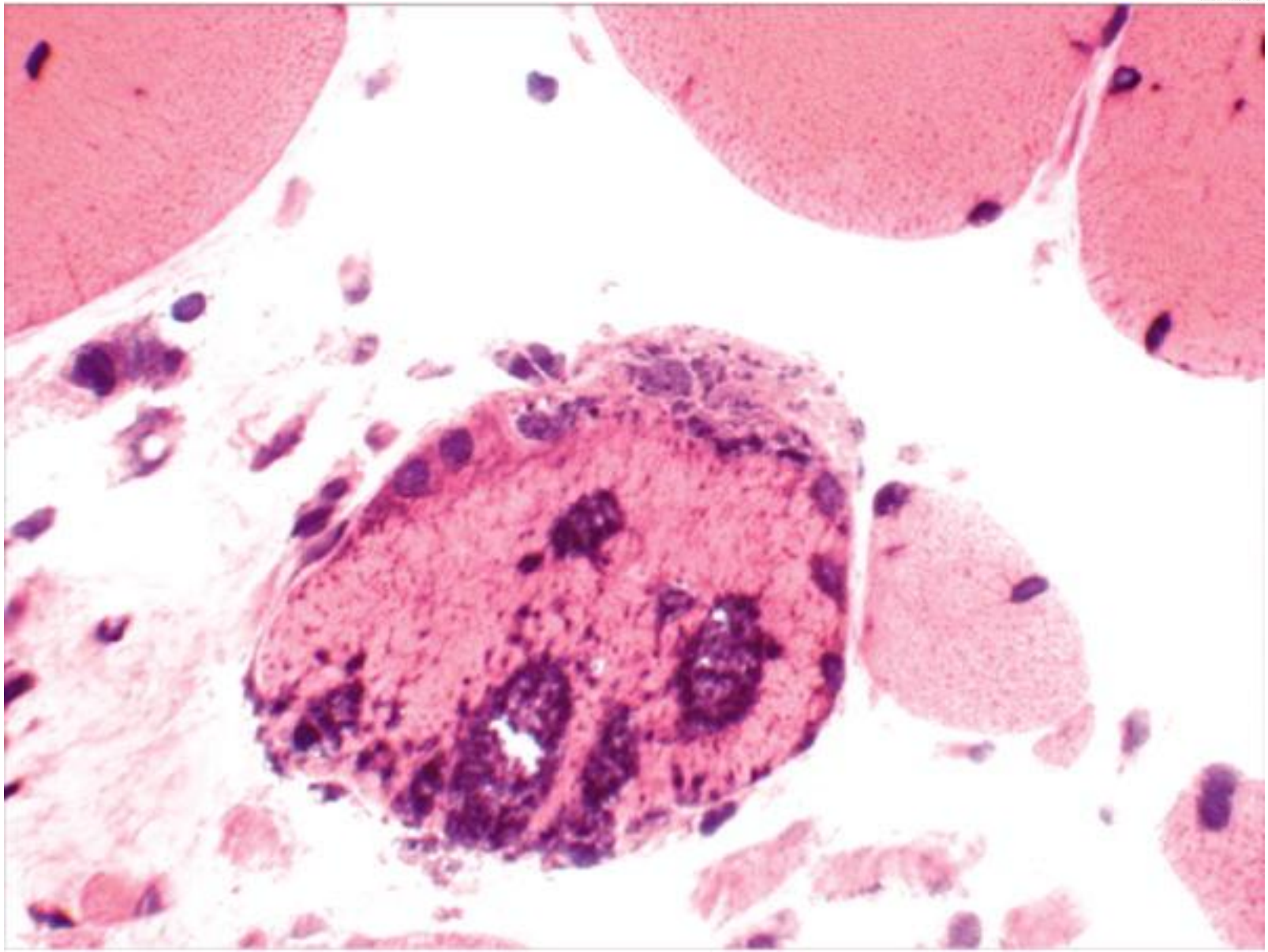
- Neither prednisone nor any other form of immunotherapy is prescribed
- physical and occupational therapy.
- Associated with DM in 20% pts.
- Dysphagia occurs in up to 40% of patients requiring cricopharyngeal myotomy.
- Mild facial weakness 1/3 patients with IBM
- Extraocular muscles are spared.
- No sensory symptoms, evidence of a mild sensory neuropathy can be detected on clinical examination and electrodiagnostic studies in up to 30% of patients.
- Muscle stretch reflexes are normal or slightly decreased. In particular, the patellar reflexes are lost early.

# Tips on tests

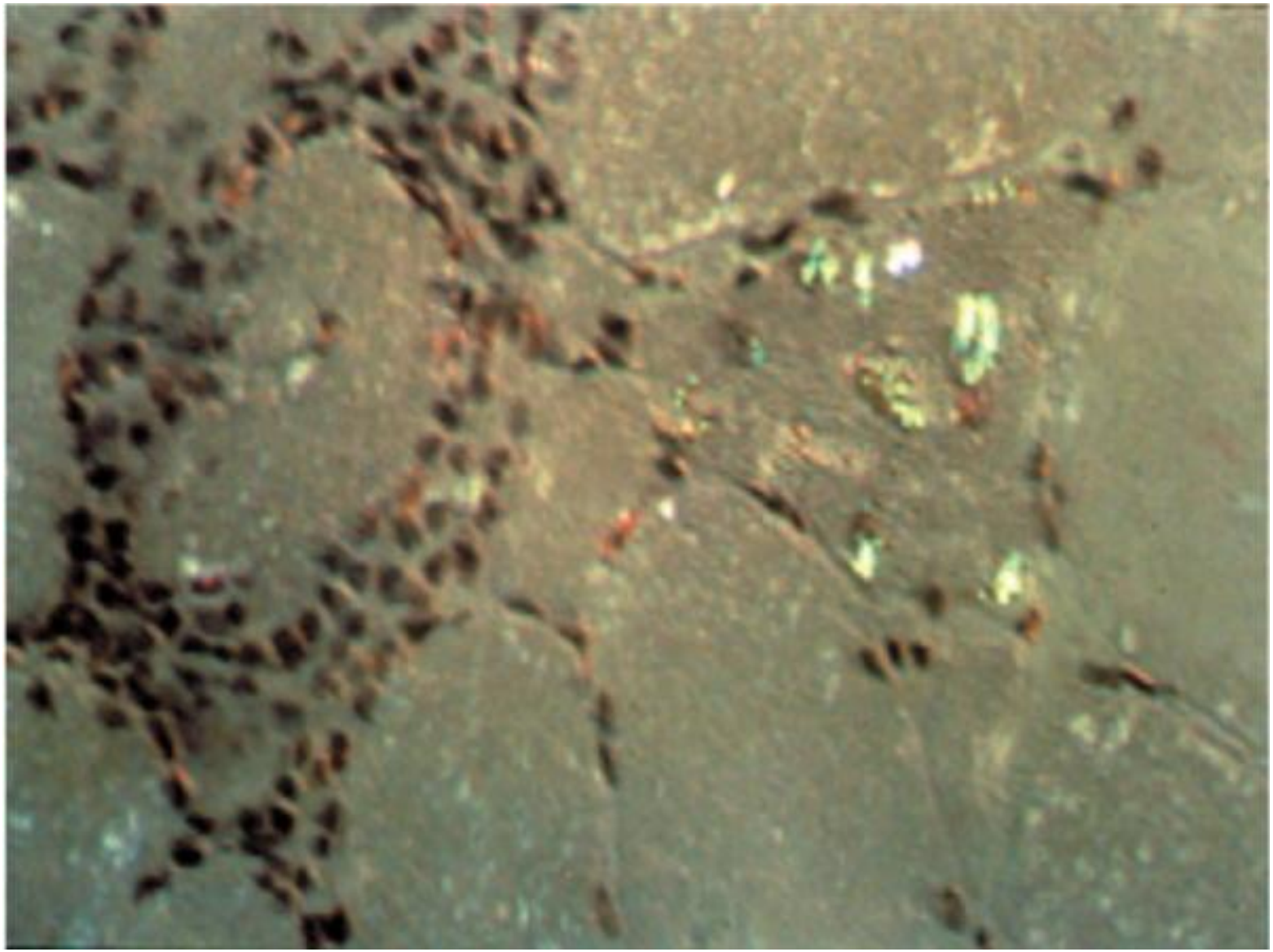
- **Blood work.** Serum CK is normal or only mildly elevated (less than 10-fold above normal). HLA DR3 phenotype (*0301/0302) occurs in IBM.
- **Electromyography.** Increased spontaneous and insertional activity, small polyphasic MUAPs, and early recruitment are usually evident on EMG. In addition, large polyphasic MUAPs can also be demonstrated in one third of patients. However, large polyphasic MUAPs can also be seen in DM, PM, and other muscle disorders (ie, muscular dystrophies) and probably reflect chronicity of the disease process rather than a neurogenic etiology.
- **Muscle imaging.** Radiological studies demonstrate atrophy and signal abnormalities in affected muscle groups.

# Histopathology

- Light microscopic: endomysial inflammation, small groups of atrophic fibers, eosinophilic cytoplasmic inclusions, and muscle fibers with one or more rimmed vacuoles lined with granular material.
- Amyloid deposition is evident on Congo red staining, using polarized light or fluorescence techniques.
- Electron microscopy demonstrates 15-nm to 21-nm cytoplasmic and intranuclear tubulofilaments .
- Macrophages and CD8+ cytotoxic/suppressor T lymphocytes, some of which invade nonnecrotic fibers.
- Gene expression studies in muscle demonstrated up-regulation of immunoglobulin genes



Muscle biopsy in patient with inclusion body myositis demonstrates a muscle fiber with a rimmed vacuole. Hematoxylin and eosin stain.



Amyloid deposition is evident with some muscle fibers in inclusion body myositis as demonstrated by Congo-red stain under polarized light

# Prognosis

- Life expectancy does not appear to be significantly altered.
- Most patients remain ambulatory, although they frequently require or at least benefit from a cane or a wheelchair for long distances.
- Some patients become severely incapacitated and require a wheelchair or become bedridden within 10 to 15 years.
- Many patients with steroid-resistant or "refractory" PM eventually are diagnosed with IBM. Importantly, some patients clinically resemble IBM, but a definitive diagnosis cannot be confirmed on muscle biopsy. These patients are diagnosed with "possible" or "probable" IBM

# Polymyositis

- Literature on PM is messed up
- Many cases of so-called PM in the literature are in fact IBM, dystrophies with inflammation, and perhaps even DM.
- Most published papers regarding epidemiology and treatment of PM have used Bohan and Peter's criteria for diagnosis of PM and DM

- Inclusion body myositis
- Dermatomyositis sine dermatitis
- Overlap syndrome (myositis with underlying connective-tissue disease)*
- Necrotizing myopathy associated with cancer or an underlying connective-tissue disease*
- Myositis associated with anti-Jo-1 or antisignal recognition particle antibodies†
- Inflammatory myopathy associated with infections (eg, human immunodeficiency virus, human T-lymphotropic virus 1, hepatitis B and C)
- Muscular dystrophies (eg, facioscapulohumeral, congenital, dysferlinopathies, and other limb-girdle dystrophies)
- Proximal myotonic myopathy (myotonic dystrophy type 2)
- Amyloid myopathy (light chain or familial)
- Metabolic myopathy with rhabdomyolysis
- Endocrine myopathies (eg, hypothyroidism, hyperparathyroidism, diabetic muscle infarction)
- Drug-induced myopathies (eg, cholesterol-lowering agents, cyclosporine, chloroquine, amiodarone, colchicine, D-penicillamine)
- Juvenile- or adult-onset spinal muscular atrophy (including Kennedy's disease)
- Polymyalgia rheumatica

*Many of these cases have histopathological features suggesting microangiopathy with so-called pipe-stem capillaries or dermatomyositis (eg, deposition of membrane attack complex, immunoglobulins, or complement on small blood vessels, or tubuloreticular inclusions in endothelial cells on electron microscopy with or without perivascular, perimysial inflammation). Patients with connective-tissue disease often are weak secondary to type 2 muscle fiber atrophy resulting from disuse or chronic administration of steroids.

†The histopathology of muscle biopsies of patients with anti-Jo-1 or antisignal recognition particle antibodies is more typical of dermatomyositis than polymyositis.

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# Clinical Features

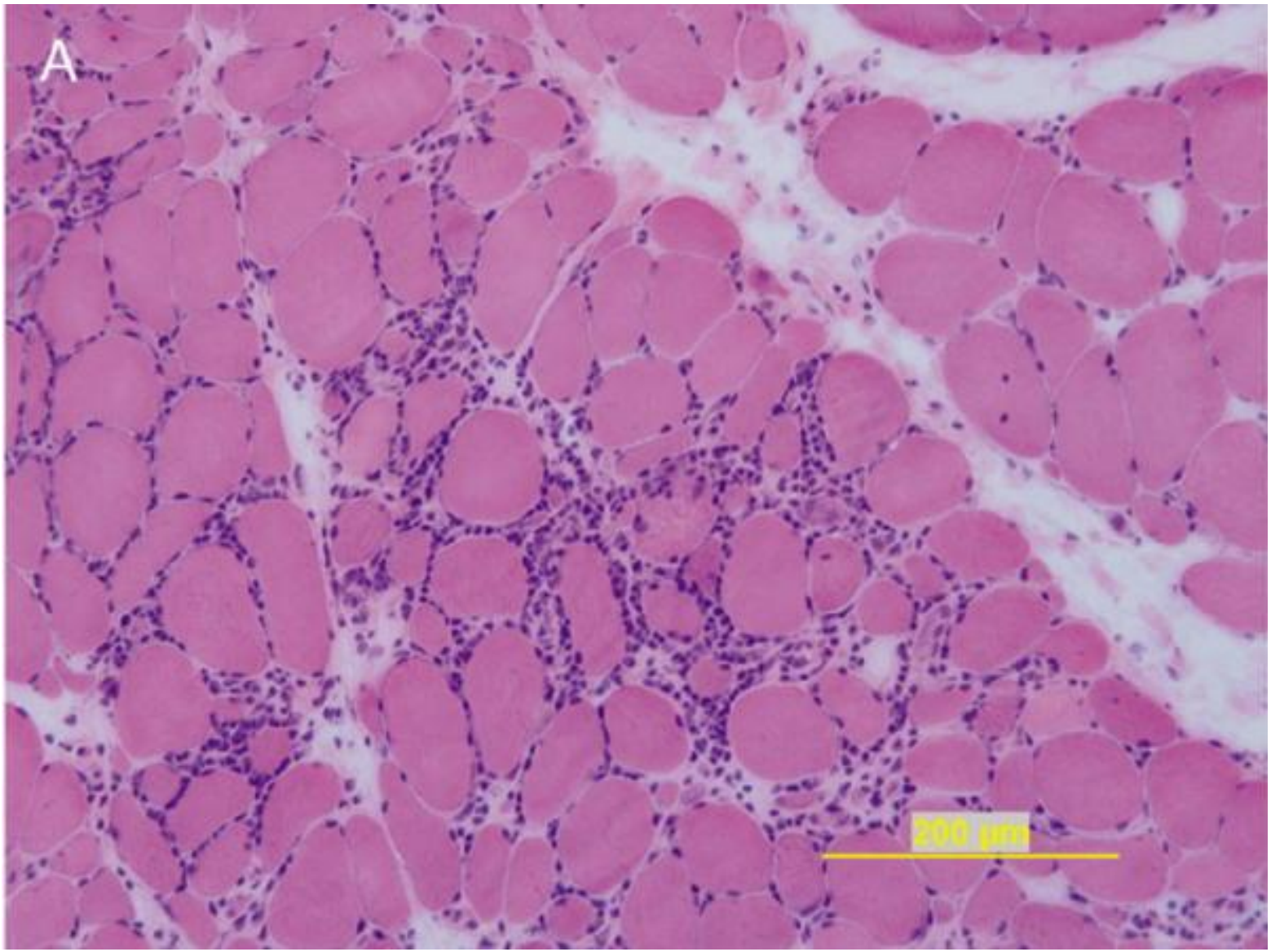
- PM over the age of 20 years and is more prevalent in females.
- Neck flexor and symmetrical proximal arm and leg weakness, which typically develops over several weeks or months. Distal muscles may also become involved but are not as weak as the more proximal muscles.
- Muscle pain and tenderness are frequently noted.
- Dysphagia reportedly occurs in approximately one third of patients secondary to oropharyngeal and esophageal involvement.
- Mild facial weakness occasionally may be demonstrated on examination.
- Sensation is normal, and muscle stretch reflexes are usually preserved.

# Diagnostic work up

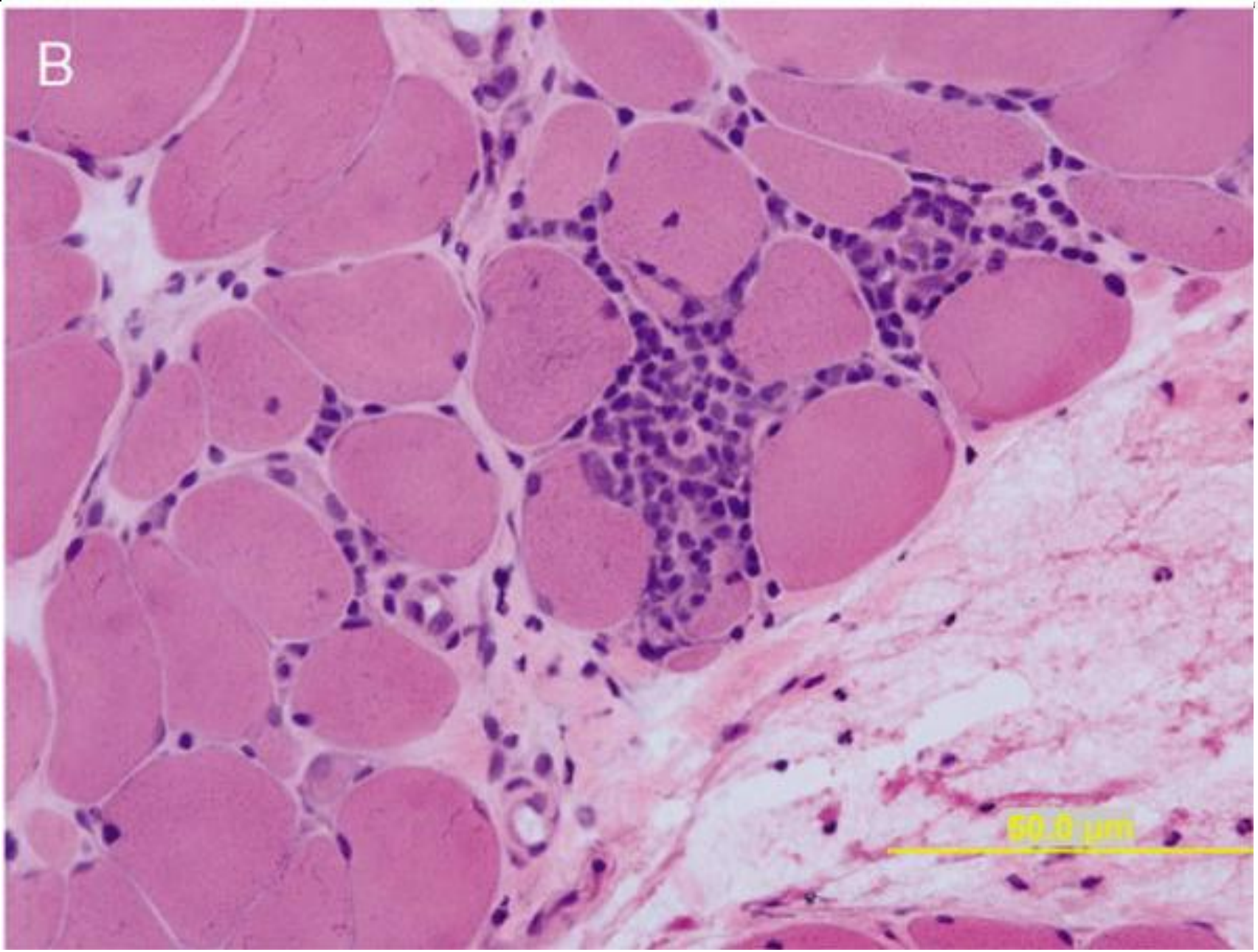
- Serum CK level is elevated fivefold to 50-fold in the majority of PM cases.
- Serum CK can be useful in monitoring response to therapy, but only in conjunction with the physical examination.
- The serum CK level does not correlate with the degree of weakness.
- Erythrocyte sedimentation rate is normal in at least half the patients and does not correlate with disease activity or severity.
- Positive ANAs are reportedly present in 16% to 40% of patients with PM.
- Imaging and EMG similar to DM

# Histopathology

- Variability in fiber size, scattered necrotic and regenerating fibers, and endomysial inflammation with invasion of nonnecrotic muscle fibers
- All of the invaded and some of the noninvaded muscle fibers may express major histocompatibility complex class 1, which is not normally present in the sarcolemma of muscle fibers.
- The endomysial inflammatory cells consist primarily of activated CD8+ (cytotoxic), α- and β- T cells, and macrophages. Investigations of the T-cell receptor repertoire of endomysial T cells in PM demonstrate an oligoclonal pattern of gene rearrangements and a restricted motif in the CD3R region of the T-cell receptor, suggesting the immune response is antigen-specific.
- In contrast to DM, no evidence of immune deposits (membrane attack complex, complement, or immunoglobulins) on the microvasculature is present in PM.
- Gene expression studies in muscle demonstrated up-regulation of immunoglobulin genes (Greenberg et al, 2002). Large numbers of plasma cells are also evident in the endomysium and sometimes surround muscle fibers (Greenberg et al, 2005a).




Endomysial inflammatory cell infiltrate is appreciated surrounding muscle fibers (*A*) and invading nonnecrotic muscle fibers (*B*). Hematoxylin and eosin stain.

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# Treatment

- Prednisone is the treatment of choice for DM and PM but not IBM,
- Initiate treatment with a short course of intravenous (IV) methylprednisolone (Solu-Medrol) (1 gram daily for 3 days) prior to starting oral doses. High-dose prednisone appears to reduce morbidity and improve muscle strength and function. Retrospective series report that 58% to 100% of patients with DM at least partially improve, while 30% to 66% respond completely with prednisone. More than 80% of patients with PM at least partially improve, but only 10% to 33% completely respond to prednisone. Noticeable clinical improvement begins within 3 to 6 months of starting prednisone in most patients with DM or PM. When no improvement is noted after an adequate trial of high-dose prednisone, other alternative diagnoses (eg, IBM or an inflammatory muscular dystrophy) and a repeat muscle biopsy should be considered.
- In patients with DM, PM, presumed autoimmune necrotizing myopathy, and other idiopathic inflammatory myositides other than IBM, the authors initiate treatment with single-dose prednisone (1.5 mg/kg up to 100 mg) every morning (**Case 5-3**). After 2 to 4 weeks of daily prednisone, a switch is made directly to alternate-day dosing (ie, 100 mg every other day). Patients with more severe disease may need to be slowly tapered to alternate-day dosing over 2 to 3 months (eg, decrease alternate dose by 10 mg every week until they are on 100 mg every other day). Patients are followed initially at least every 2 to 4 weeks. High-dose prednisone is maintained until patients are back to normal strength or until improvement in strength has reached a plateau (usually 4 to 6 months). Subsequently, the prednisone dose is slowly tapered by 5 mg every 2 to 3 weeks. Once the dose is reduced to 20 mg every other day, the prednisone is tapered no faster than 2.5 mg every 2 weeks.

| Disorder | Dermatomyositis | Polymyositis | Inclusion Body Myositis |
|---|---|---|---|
| Sex | Female > male | Female > male | Male > female |
| Age of onset | Childhood and adult | Adult | Elderly (> 50 years) |
| Rash | Yes | No | No |
| Pattern of weakness | Proximal > distal | Proximal > distal | Proximal = distal; predilection for finger/wrist flexors, knee extensors |
| Serum creatine kinase | Normal or increased (up to 50 times normal) | Increased (up to 50 times normal) | Normal or mildly Increased (< 10 times normal) |
| Muscle biopsy | Perivascular, perimysial, and endomysial infiltrates; perivascular/ perimysial $CD4^+$ dendritic cells and B cells; endomysial PCD; MXA, MAC, Ig, C deposition on vessels | Perivascular, perimysial, and endomysial infiltrates; endomysial $CD8^+$ T cells invade nonnecrotic fibers expressing MHC1 antigen; endomysial macrophages, MDC, and PC | Perivascular, perimysial, and endomysial infiltrates; $CD8^+$ T cells invade nonnecrotic fibers expressing MHC1 antigen; muscle fibers with rimmed vacuoles; amyloid deposits; also COX-negative fibers; endomysial macrophages, MDC, and PC; electron microscopy: 15-nm to 18-nm tubulofilaments |
| Response to immunosuppressive therapy | Yes | Yes | None or minimal |
| Common associated conditions | Myocarditis, interstitial lung disease, malignancy, vasculitis, other connective-tissue diseases | Myocarditis, interstitial lung disease?, other connective-tissue diseases | Sensory neuropathy, paraproteinemia, autoimmune disorders (Sjögren syndrome, sarcoidosis, thrombocytopenia) |

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