Myopathies

Introduction and Review of Muscles

Skeletal muscle is made up of **muscle** and **connective tissue**. The connective tissue is named according to the muscle unit it surrounds. The **endomysium** is the smallest unit of connective tissue and it surrounds individual **muscle fibers.** When fibers are combined they're called **bundles**. Bundles are surrounded by **perimysium**. When bundles come together it's the gross anatomy thing we think of as **muscle**. Muscle is surrounded by **epimysium. Muscle** is in G_0; the fibers are permanent. They cannot be healed. Hypertrophy and atrophy are the only two possible outcomes. If necrosis occurs, or inflammation damages the muscle to a scar, there is no coming back.

Disorders of skeletal muscle will demonstrate themselves as **weakness**, and that weakness can be with or without pain. **Tender weakness** is indicative of inflammatory myopathy. **Painless weakness** is noninflammatory. However, be careful with jumping to this one symptom—painless weakness may also be disorders of the endplate or neurons.

Inflammatory Myopathies

The inflammatory myopathies are, as the name suggests, inflammation of the skeletal muscle. This inflammation causes muscle damage and weakness. **Inflammation** usually hurts, and inflammation of the skeletal muscle causes serologic evidence of muscle damage. All inflammatory myopathies will present with an **elevated creatinine kinase**, a marker of skeletal muscle damage, as well as inflammatory markers. There are both nonspecific (CRP, ESR, ANA, RF, etc.) and specific (**anti-Jo** and **anti-Mi** antibodies) inflammatory markers.

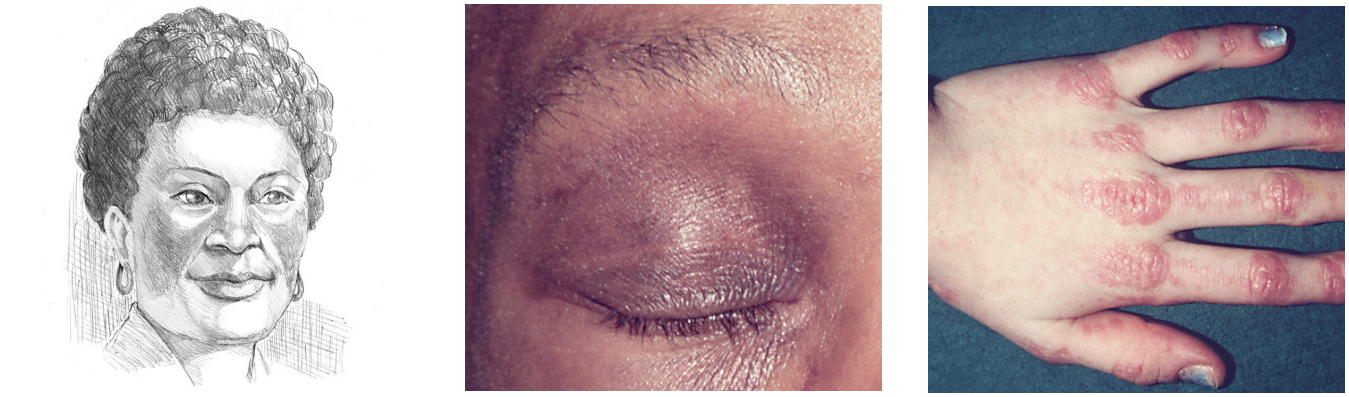
Each of the three inflammatory myopathies—dermatomyositis, polymyositis, and inclusion body myositis—has distinct features that will help separate them. However, these syndromes overlap, and the only definitive way to separate these disorders is on the **biopsy**. Pay attention to the inflammatory pathogenesis and the biopsy findings.

The location of the inflammation relative to the muscle bundles will help inform whether another finding can be expected. For example, deep inflammation of endomysium could not cause skin findings, while superficial inflammation of the epimysium could.

Inflammatory Myopathy: Dermatomyositis

In **dermato** (skin) **myos** (muscle) **itis** (inflammation), both the skin and muscles are involved. This can be explained by the region of inflammation: the perimysium and **epimysium**. The epimysium is at the **outer edge** of the muscle, meaning "just underneath the skin." Dermatomyositis presents with **symmetrical proximal muscle weakness**, as is expected from an inflammatory myopathy, and the muscles are **tender** because of the inflammation. It can present with a variety of skin findings. Facial rashes are common, such as the heliotrope rash, an erythematous to violaceous rash on the eyelids (Figure 13.1b). More diffuse facial erythema can occur, similar to the malar rash seen in lupus (Figure 13.1a), but in dermatomyositis, the nasolabial folds are not spared. Gottron's papules, **red papules** on the knuckles, elbows, or knees, may occur, as well as the "**shawl sign**," an erythematous rash that appears to be draped over the patient's shoulders.

The workup will include positive serologic evidence of muscle breakdown and inflammation. The **biopsy** will reveal **peripheral atrophy** and **leukocytes** invading the **epimysium** and the nearby muscle tissue. Dermatomyositis is **responsive to steroids**.

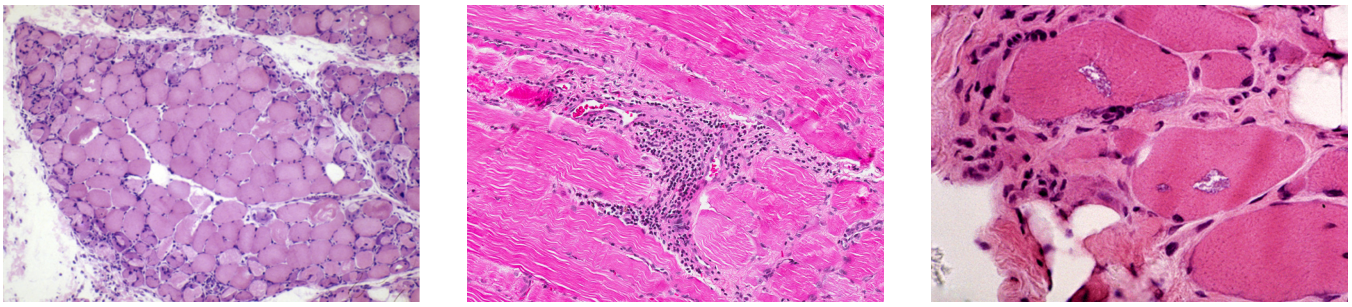


(a) (b) (c)

Figure 13.1: Skin Findings in Dermatomyositis
(a) Malar rash appears as erythema in a butterfly-shaped pattern across the face, sparing the nasolabial folds. (b) Heliotrope rash appears as an erythematous to violaceous rash on the eyelids. (c) Gottron's papules are erythematous, appearing across the knuckles of the hand.

Inflammatory Myopathy: Polymyositis

Polymyositis is another inflammatory myopathy caused by inflammation of the **endomysium**. But unlike dermatomyositis, because there is no inflammation of the muscle or connective tissue near the skin, polymyositis will have **no skin findings**. However, there are many commonalities. **Tender** or **painful symmetrical proximal muscle weakness is present**. The serologic markers of muscle damage and inflammation will be, too. A **biopsy** of the muscle will reveal **central necrosis**, deep within fascicles, surrounded by **cytotoxic CD8 T cells**.



(a) (b) (c)

Figure 13.2: Histopathologic Diagnosis of Inflammatory Myositis
(a) Dermatomyositis shows epimysial inflammation (lots of little blue dots which are the inflammatory cells) surrounding atrophying skeletal muscle fibers, at the edge of the muscle slice. The deeper muscles are unaffected. (b) Polymyositis shows endomysial inflammation (lots of little blue dots are the inflammatory cells) surrounding necrotic skeletal muscle fibers in the middle of the muscle. (c) Inclusion body myositis shows inclusion bodies (empty, moth-eaten vacuoles) at high magnification.

Inflammatory Myopathy: Inclusion Body Myositis

Despite being an inflammatory myopathy, this version of myositis is **nontender**, **asymmetric**, and often involves the **distal** muscles. It almost sounds like a disorder of the neuromuscular junction, but will not be diagnosed on electromyography (EMG) or nerve conduction velocity (NCV) studies. When a biopsy is taken, the pathognomonic **necrosis of skeletal muscle** with **vacuoles** (the inclusion bodies) will be seen. This inflammatory myopathy is **refractory to steroids**.

X-Linked Muscular Dystrophy/Duchenne's

Duchenne's is an eponym that you are unlikely to see on the test, but is commonly used to describe the condition. It is a **degenerative** disorder characterized by muscle wasting, where the **skeletal muscle is replaced by adipose tissue**. It's **X-linked recessive**, so it will affect **boys** far more often than girls. Because it's recessive, it must be caused by a loss-of-function mutation, a **deletion** of the gene that codes for **dystrophin**, the largest gene in the human genome. Because it is the largest gene, with the largest number of nucleotides, it has the highest risk for getting messed up. Dystrophin is a cell membrane protein that allows for interaction of the muscle fiber with the extracellular matrix. When it fails, adipose replaces the muscle, though the mechanism is still unclear. It is **progressive**, from **proximal skeletal muscle** outward toward the distal muscles.

Presenting around **1 year of age**, Duchenne's affects the quadriceps first, which makes it difficult for the child to start walking. **Infiltration of calf muscles with fat** is called **pseudohypertrophy.** The combination of quadriceps atrophy making the thighs small and the invasion of adipose into the calf muscles making them big, creates the appearance of large muscular calves. The progression is hips, shoulders, then distending outwards distally before turning towards the muscles of the chest. **Gower's sign** is the unusual way in which a child will use a series of hand pushes to rise from the ground, unable to rely on the hip flexors or shoulder muscles. This will eventually result in a **complete loss of muscle tone** and the inability to move. Total paralysis always sets in by the end of the second decade (~20 years old). **Death** occurs as a result of **myocardial infiltration**, though the diaphragm can be affected as well.

A biopsy will reveal **skeletal muscle** intersected with **adipose** tissue. Never should the two be in the same slide except for this disease. There is no treatment.

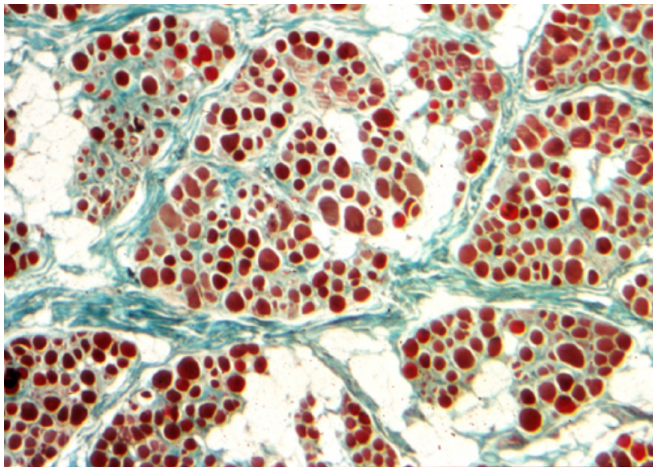


Figure 13.3a: X-Linked Muscular Dystrophy
Histology showing skeletal muscle being replaced with adipose.

Figure 13.3b: X-Linked Muscular Dystrophy
A living patient with calf pseudohypertrophy.

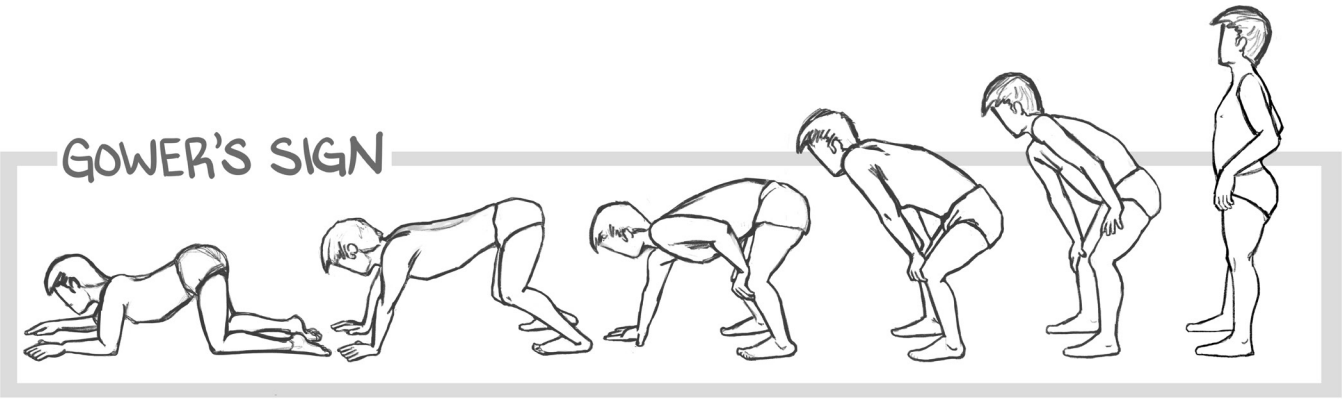


Figure 13.3c: X-Linked Muscular Dystrophy
Artist's rendition of Gower's sign, where the child will walk up his legs with his arms to go from prone to standing.

Becker's Muscular Dystrophy

It's the same disease as Duchenne's except that there's merely a **mutation** of the dystrophin gene rather than a deletion. Because there is some protein (albeit dysfunctional) as opposed to none, this disease is often milder. The onset is much later, the course variable based on the mutation and levels of dystrophin produced. Becker's rarely affects the heart or diaphragm, so these patients can live a near-normal lifespan.

Citations

Figure 13.1a: National Institute of Arthritis and Musculoskeletal and Skin Diseases. "Butterflyrash." 2009. Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Butterflyrash.jpg.

Figure 13.1b: International Myositis Assessment and Clinical Studies Group (IMACS). "Heliotrope rash." Classification Criteria for Idiopathic Inflammatory Myopathies. http://www.imm.ki.se/biostatistics/calculators/iim/Heliotrope.jpg.

Figure 13.1c: Dugan, Elizabeth M., Adam M. Huber, Frederick W. Miller, and Lisa G. Rider. "Dermatomyositis." 2009. Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Dermatomyositis.jpg.

Figures 13.2a, 13.2b, 13.2c: Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license granted by The UAB Research Foundation.

Figure 13.3a: "DMD. Advanced DMD. Severe loss of muscle with fat replacement and fibrosis." neuropathology-web.org. n.d. http://neuropathology-web.org/chapter13/images13/13-12l.jpg.

Figure 13.3b: Senanayake, Hemal M. S., Anujaya D. Dedigama, Randil P. De Alwis, and Kanapathipillai Thirumavalavan. (2014). Hoffmann syndrome: A case report. International Archives of Medicine 7.2 (2014). 7. 2. 10.1186/1755-7682-7-2.