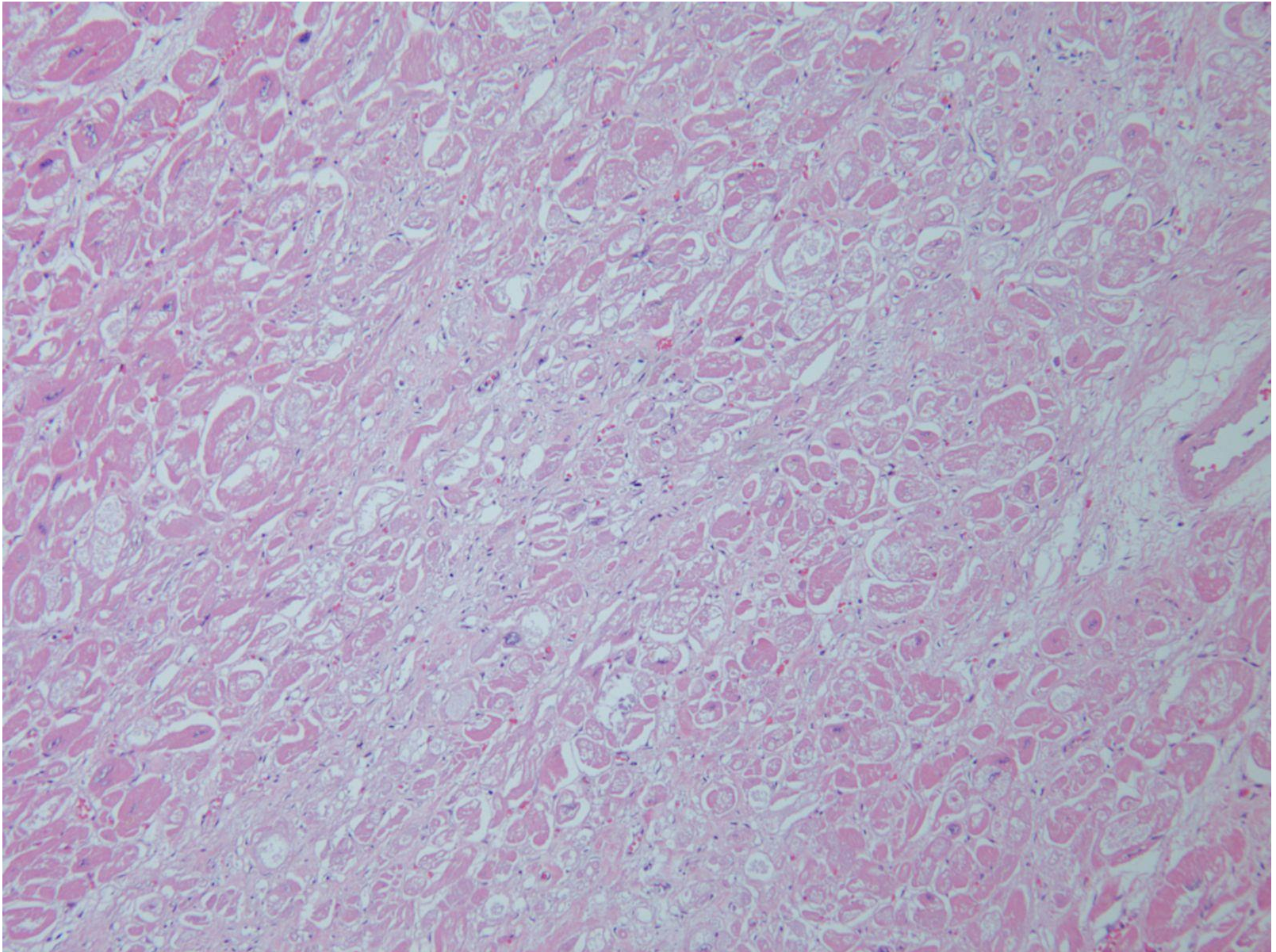
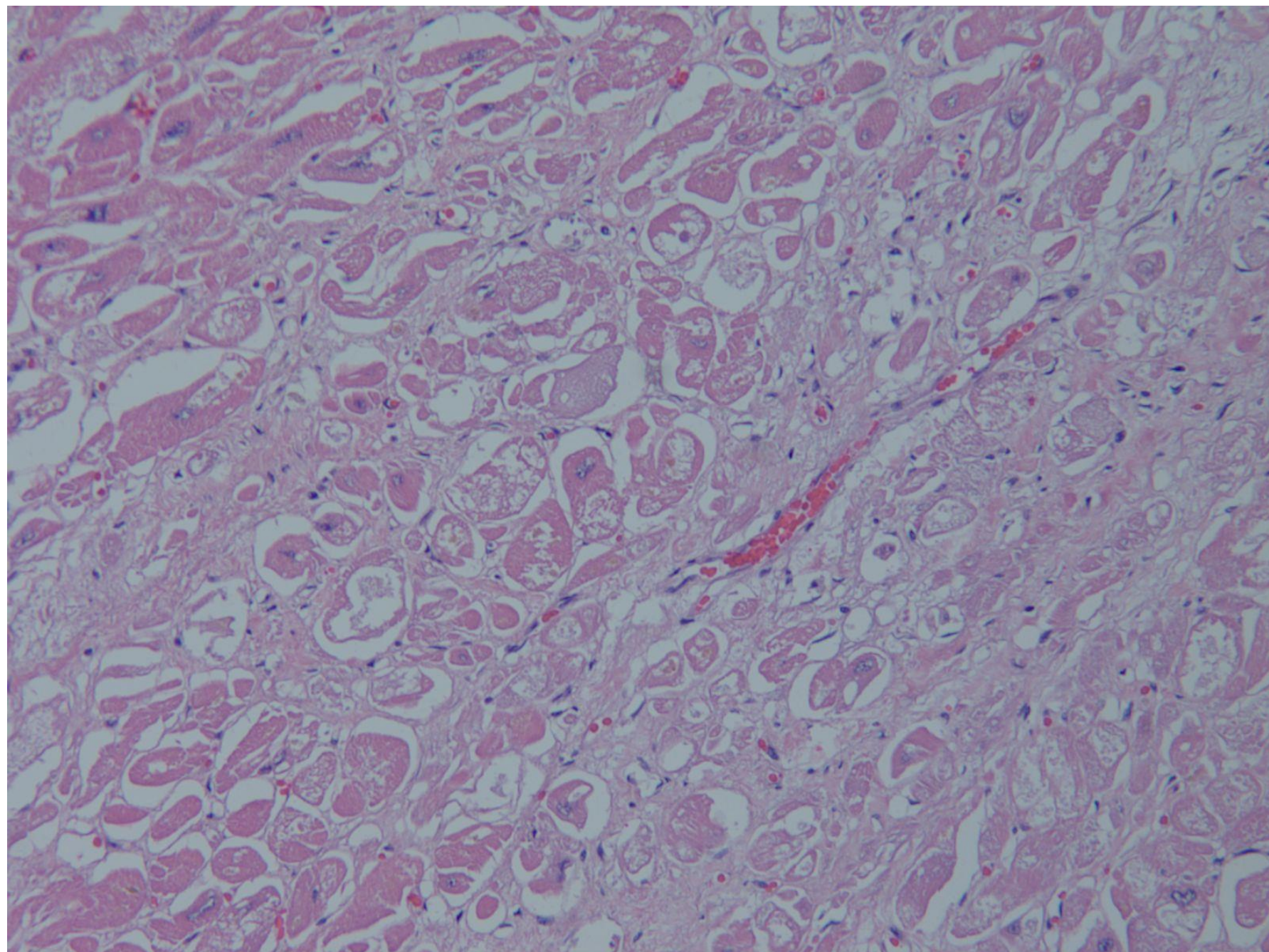


Case History:

A 73-year-old woman was found dead at home by her husband. Her past medical history included shingles, hypertension, chronic pain, progressive systemic sclerosis, “CREST” syndrome, osteoarthritis, and osteoporosis. At autopsy, the heart weighed 510 grams and had dilation of the left ventricular cavity. Microscopic sections of the heart are shown. Toxicological analysis revealed the presence of acetaminophen (20 mg/L) and hydroxychloroquine (39,000 ng/mL).



Case courtesy of Dr. Varsha Podduturi (Harris County ME, Houston TX)



What underlying disease or process is most likely involved in this case?

- A. Drug induced cardiomyopathy
- B. Fabry disease
- C. Ischemic heart disease
- D. Danon disease
- E. Pompe disease

A. Drug induced cardiomyopathy (CORRECT ANSWER, 61.08% responses)

The histologic findings in this case are related to hydroxychloroquine (HCQ), which is used for treatment in rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, and Sjogren syndrome as well as treatment for malaria. The most widely accepted proposed mechanism includes disruption of the lysosomal autophagy pathway by inhibiting lysosome-autophagosome fusion which leads to build up of metabolic products in the cytosol. HCQ cardiotoxicity can occur in acute use by blocking sodium, calcium, and potassium channels which can cause tachyarrhythmias. In chronic use, chronic rhythm abnormalities occur due to damage to the conduction system. Left ventricular hypertrophy or biventricular or biatrial dilatation with concentric hypertrophy with a restrictive filling pattern can be seen with long-term HCQ use. On histologic examination, vacuolated myocytes are the most common finding. Electronic microscopy reveals myeloid and curvilinear bodies (see attached images), which are inclusions made of whorled layers of alternating dense and pale material made of glycolipids and glycoproteins. The presence of curvilinear inclusion bodies can help differentiate between HCQ cardiomyopathy and Fabry disease.

B. Fabry disease (17.3% responses)

Fabry disease is an X-linked recessive lysosomal storage disease caused by decreased or absent lysosomal alpha-Galactosidase A activity. This results in an accumulation of glycosphingolipids in lysosomes in various tissues including the vascular endothelium, kidneys, eyes, skin and nervous system. It most often occurs in males and usually has its onset in childhood or adolescence. Other clinical manifestations include heat intolerance with decreased sweating and cutaneous angiokeratomas. Cardiac manifestations include a restrictive cardiomyopathy that is due to glycosphingolipid accumulation in the myocytes and conduction tissue. Hypertrophic myocytes contain vacuoles laden with sphingolipids, resulting in eventual fibrosis. On electron microscopy, myeloid bodies are seen, which are inclusions consisting of whorled layers of alternating dense and pale material composed of accumulated glycolipids and glycoproteins due to inhibition of intralysosomal α -galactosidase A activity. These are also seen in patients with other metabolic disorders and most patients with HCQ and CQ toxicity. Unlike in HCQ induced cardiomyopathy, there will be no curvilinear bodies seen on EM.

C. Ischemic heart disease (13.51% responses)

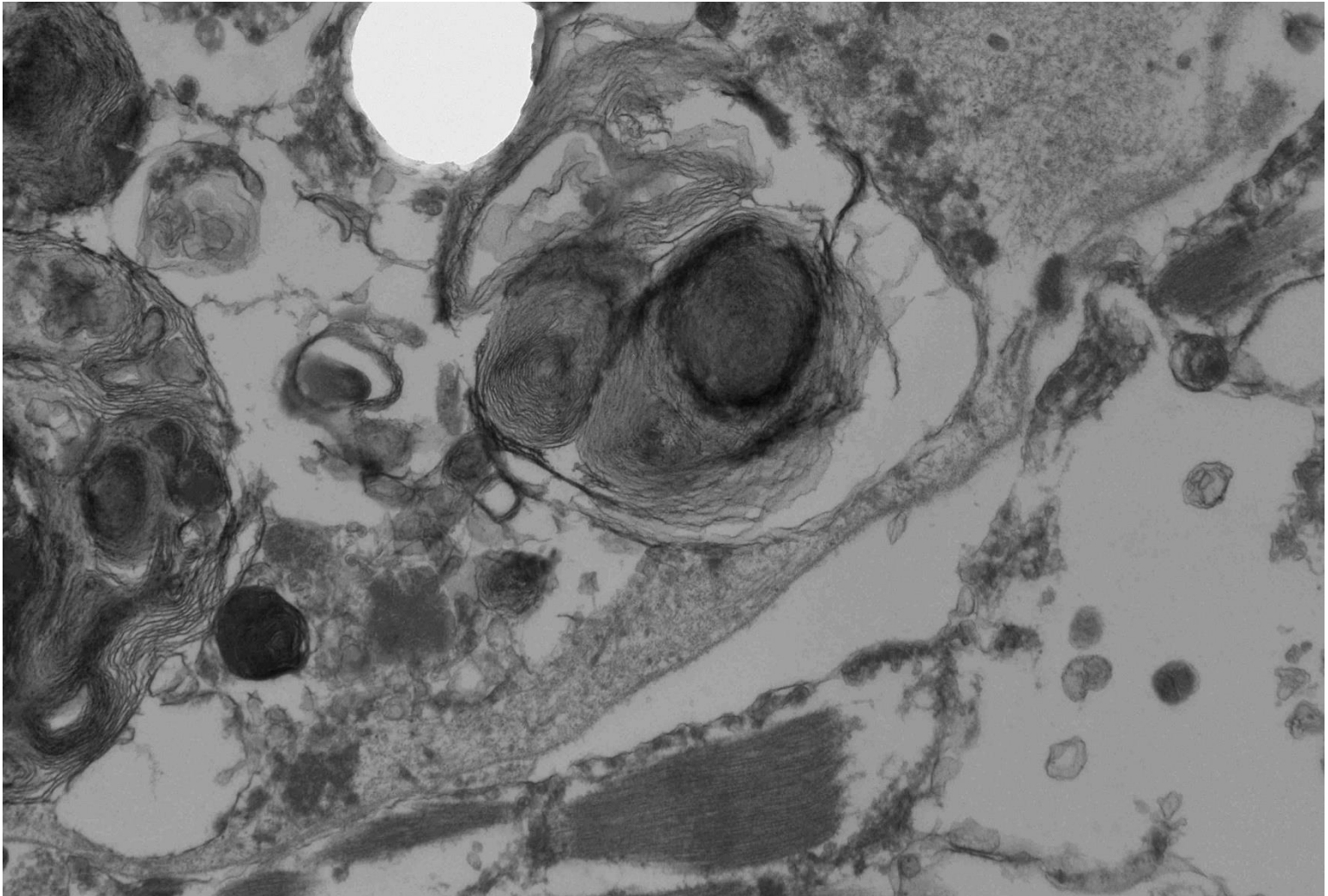
Ischemic heart disease can result in vacuolar degeneration, which is vacuolization of the muscle fibers that results resulting in an empty appearing nucleus within a sarcolemmal tube. The empty spaces within the nucleus are thought to represent glycogen, water, or lipids. It most often occurs in the left ventricular subendocardium, at the periphery of myocardial infarcts, and in the perivascular regions within the myocardium.

D. Danon disease (3.78% responses)

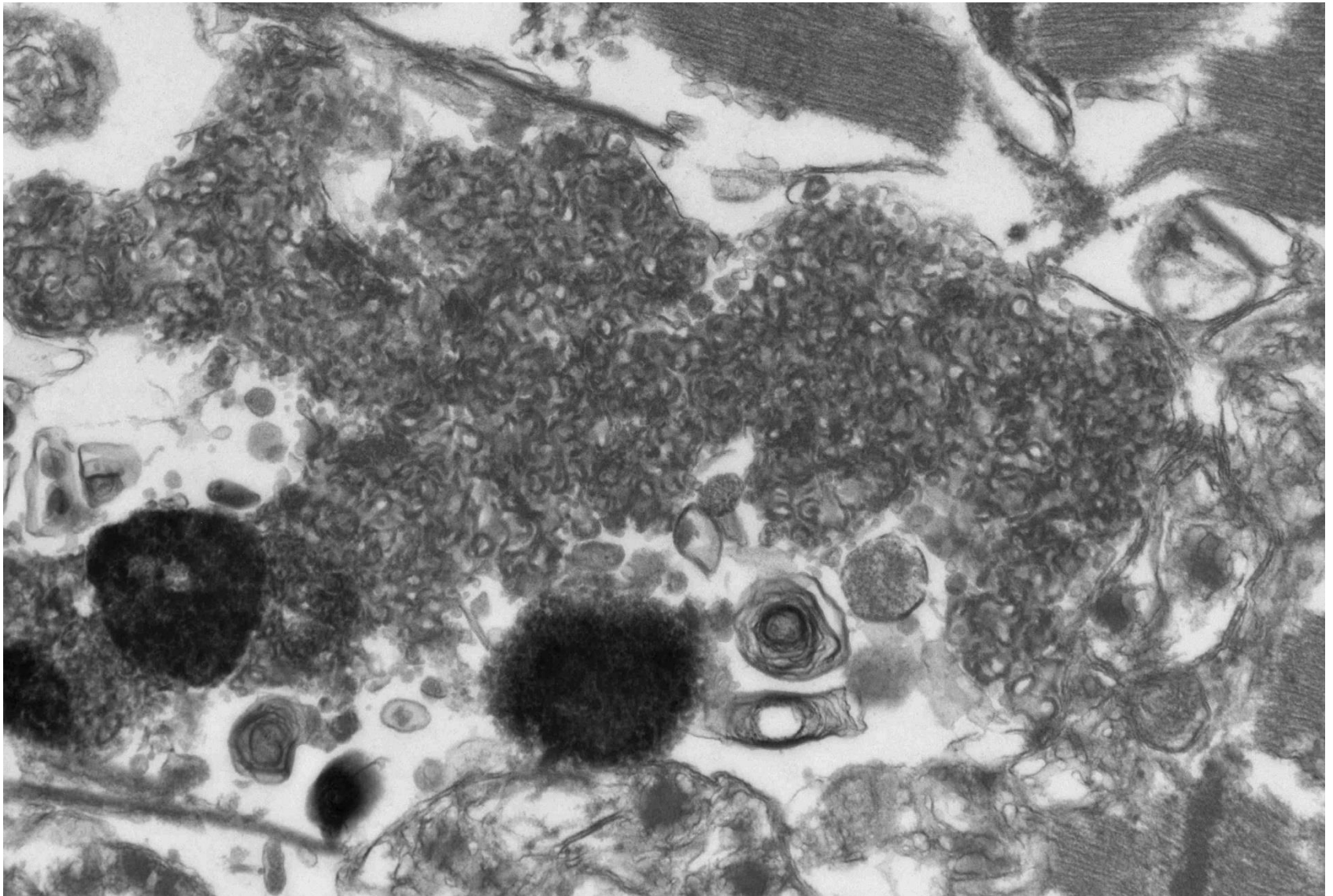
Danon disease is a rare X-linked dominant disorder that results from a genetic mutation in the lysosomal associated membrane protein 2 (LAMP2) gene. Clinical features include a triad of cardiomyopathy, skeletal disease, and intellectual disability. Males are affected earlier and more severely affected than females and usually present with hypertrophic cardiomyopathy in childhood. Classic cardiac involvement includes a hypertrophic cardiomyopathy, although dilated and restrictive cardiomyopathy have also been reported. Histology reveals scattered vacuoles that stain positive for periodic acid-Schiff (PAS) stain. EM shows autophagic vacuoles and excess glycogen.

E. Pompe disease (4.32% responses)

Pompe disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of acid alpha-glucosidase deficiency (GAA), which is a lysosomal glycogen-hydrolyzing enzyme. This is the only glycogen storage disease that is also classified as a lysosomal storage disease. This results in the accumulation of glycogen accumulation in skeletal, cardiac, and smooth muscle tissues. The clinical presentation ranges from an infantile form to an adult-onset form. Patients with infantile Pompe disease present within the first few months of life with hypotonia. Late onset Pompe disease can present at any age, and present with symptoms related to proximal lower extremities and paraspinal trunk muscles (such as hip adductor weakness) and respiratory insufficiency (related to problems with the diaphragm and accessory muscles of respiratory). Histology will also reveal myocyte vacuolization. Measurement of GAA activity in skin fibroblasts is the current gold standard for diagnosis.



Myeloid bodies (8000x)



Curvilinear bodies (12000x)

References:

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Chatre C, Roubille F, Vernhet H, et al. Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature. *Drug Saf*. 2018; 41: 919-931.