Propionic acidemia

Propionic acidemia or propionyl-CoA carboxylase deficiency (PCC deficiency), is a rare autosomal recessive metabolic disorder, classified as a branched-chain organic acidemia. PCC located in the mitochondrial matrix is required for the normal breakdown of both the essential amino acids (valine, isoleucine, threonine and methionine) and certain odd-chained fatty-acids. The disorder presents in the early neonatal period with poor feeding, vomiting, lethargy, and lack of muscle tone. In the late onset form, the affected children manifest intellectual disability, autism, chronic kidney disease or cardiomyopathy. Propionic acidemia causes an accumulation of dangerous acids (metabolic acidosis) and toxins (ketones and ammonia) to damage to a variety of organs, including the brain, heart, kidney, liver and striated muscles. The disease has been called as ketotic hyperglycinemia. Symptoms commonly show up during the first weeks of life: They are related to mitochondrial disorders, and are characterized by decreased mitochondrial respiration.

Ref.-1: GARD (Genetic and Rare Disease Information Center). Propionic acidemia. https://rarediseases.info.nih.gov/diseases/467/propionic-acidemia

Ref.-2: Marchuk H, et al. Pathophysiological mechanisms of complications associated with propionic acidemia. Pharmacol Therap 2023; 249: 108501. doi: 10.1016/j.pharmthera.2023.108501

Propionyl-CoA carboxylase (PCC)

Propionyl-CoA carboxylase (PCC), a biotinylated mitochondrial enzyme essentially, is composed of a 750 kDa alpha(6)-beta(6)-dodecamer with $\alpha 6 \beta 6$ structure. PCC catalyzes the carboxylation reaction of propionyl-CoA to yield methylmalonyl-CoA in the mitochondrial matrix. This is one of many steps in the process of converting certain amino acids and fats into energy. Propionyl-CoA is the end product of odd-chain fatty acid metabolism, including most methylated fatty acids. The amino acids valine, isoleucine, threonine and methionine are also substrates for propionyl-CoA metabolism. Mutations in the PCC gene, either in the α subunit (PCCα) or β subunit (PCCβ), can cause propionic acidemia in humans.

Ref.: Wongkittichote P, et al. Propionyl-CoA carboxylase. A review. Mol Genet Metab 2017; 122(4): 145-152. doi: 10.1016/j.ymgme.2017.10.002

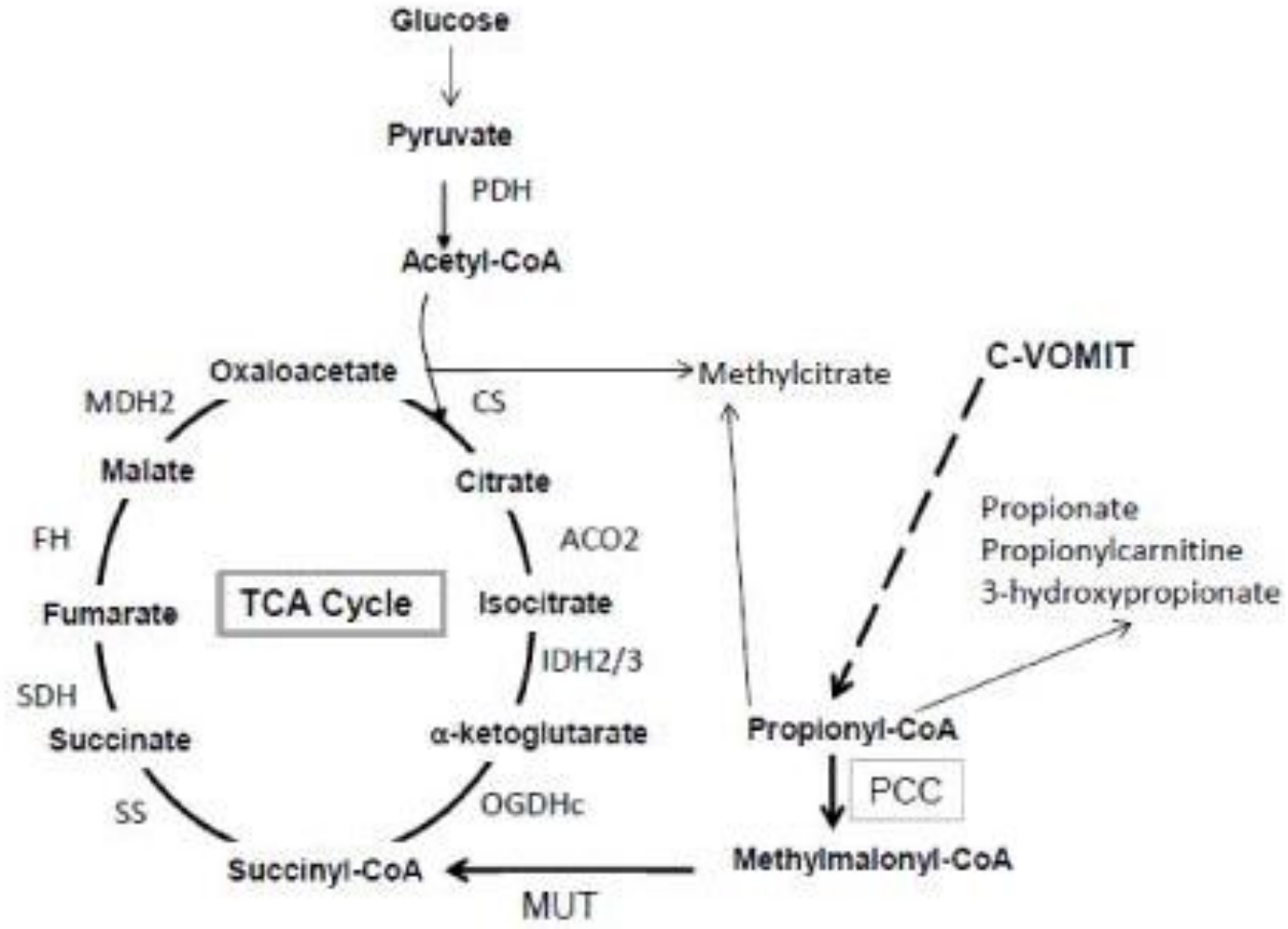


Diagram of TCA cycle and propionate pathways

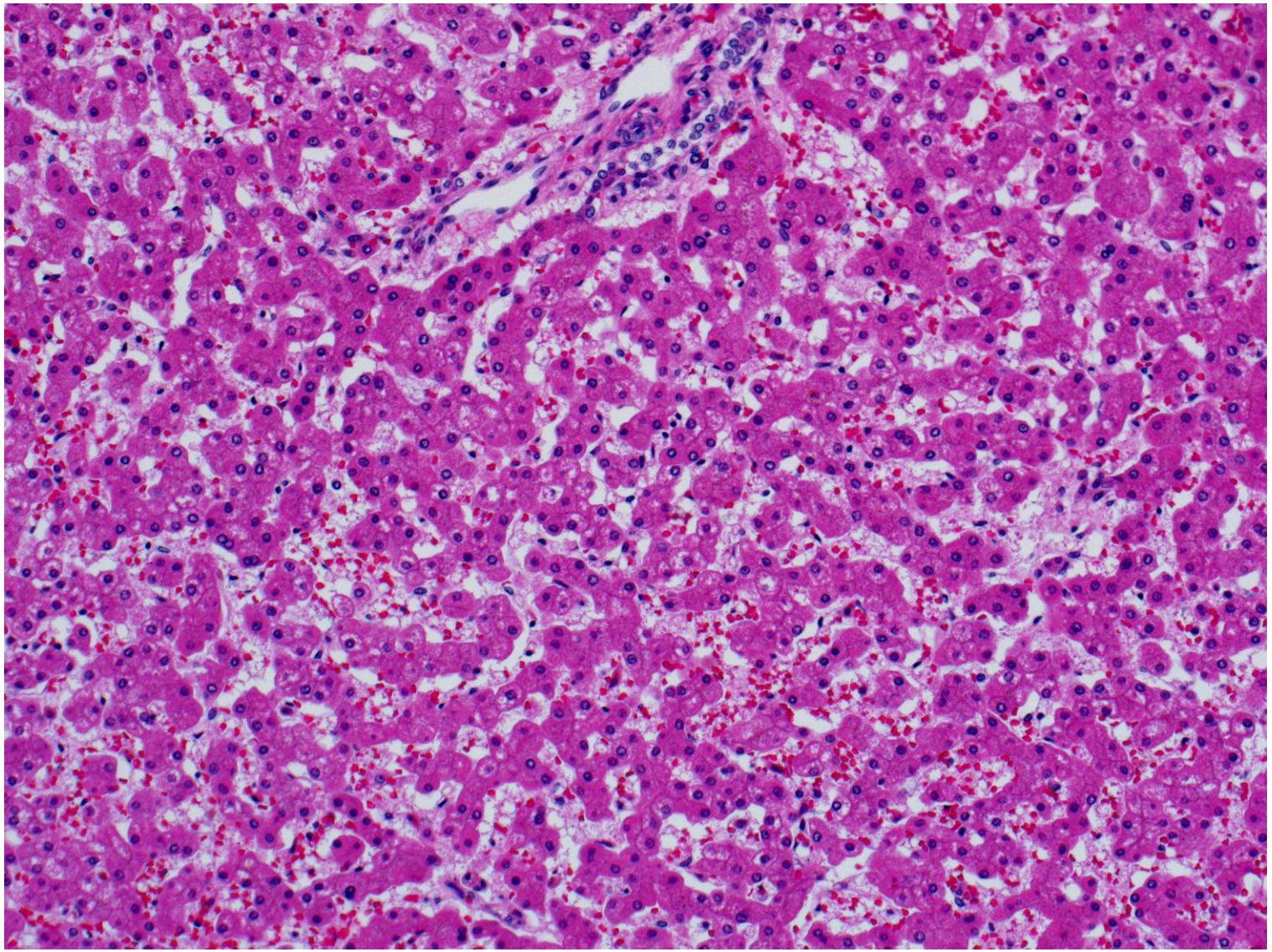
PDH: pyruvate dehydrogenase complex, CS: citrate synthase, ACO2: mitochondrial aconitase, IDH2/3: mitochondrial isocitrate dehydrogenase 2 and 3 (NAD/NADP), OGDHc: 2-oxoglutarate dehydrogenase complex, C-VOMIT: cholesterol, odd chain fatty acids, methionine, isoleucine, threonine, **PCC: propionyl-CoA carboxylase**, MUT: methylmalonyl-CoA mutase, SS: succinate synthase (succinyl-CoA ligase), SDH: succinate dehydrogenase, FH: fumarase, MDH2: mitochondrial malate dehydrogenase.

Borrowed from: Wongkittichote P, et al. Propionyl-CoA carboxylase. A review. Mol Genet Metab 2017; 122(4): 145-152. doi: 10.1016/j.ymgme.2017.10.002

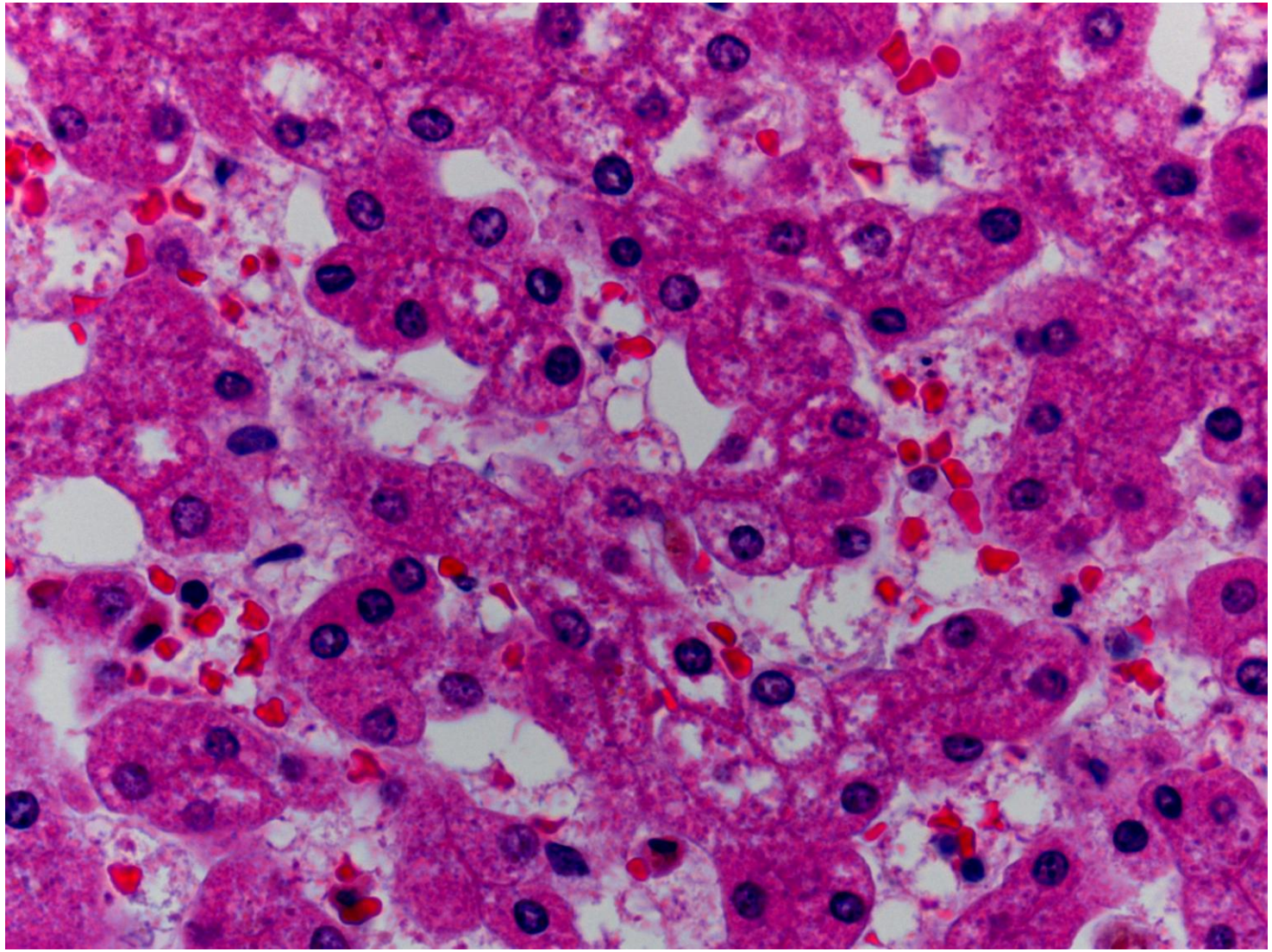
Autopsy case presentation (an 11 days-old boy)

A boy was delivered normally. At day 8, decrease of the suckling ability started. At day 10, he lost the suckling power, and acidosis and hyperammonemia were complicated. The serum ammonia levels were decreased from 1,100 to 600 μg/dL by hemodialysis, but the patient died on the day 11 because of hypoxia. Systemic edema, hypoproteinemia and insulin-resistant hyperglycemia (900 mg/dL) were complicated. Light and electron microscopic features of the autopsied organs are presented. Mitochondrial changes (swelling and vacuolation) are commonly observed.

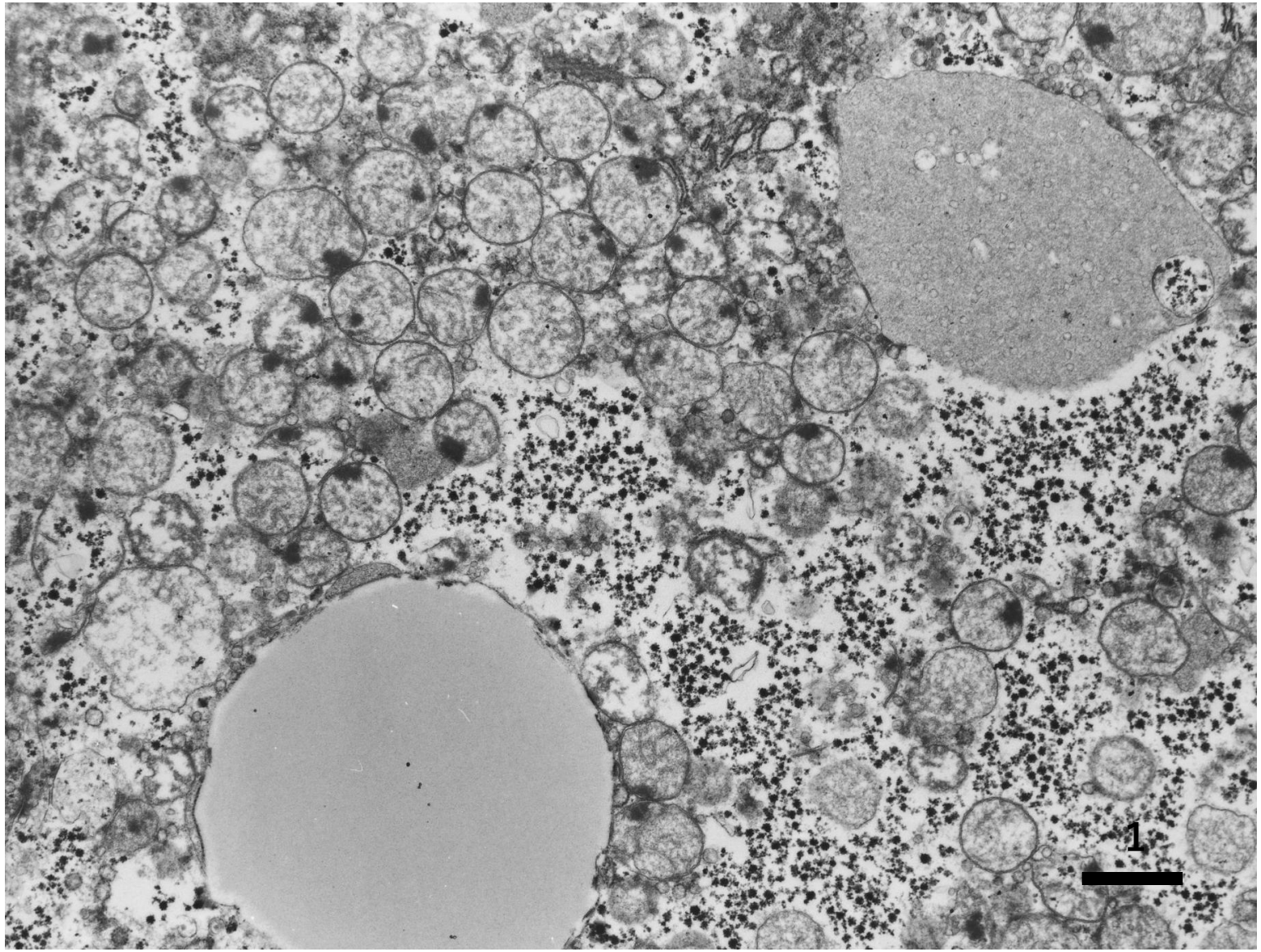
The result of tandem mass screening for newborns suggested organic acidemia. Analysis on the organic acids in the urine at day 10 indicated propionic acidemia.



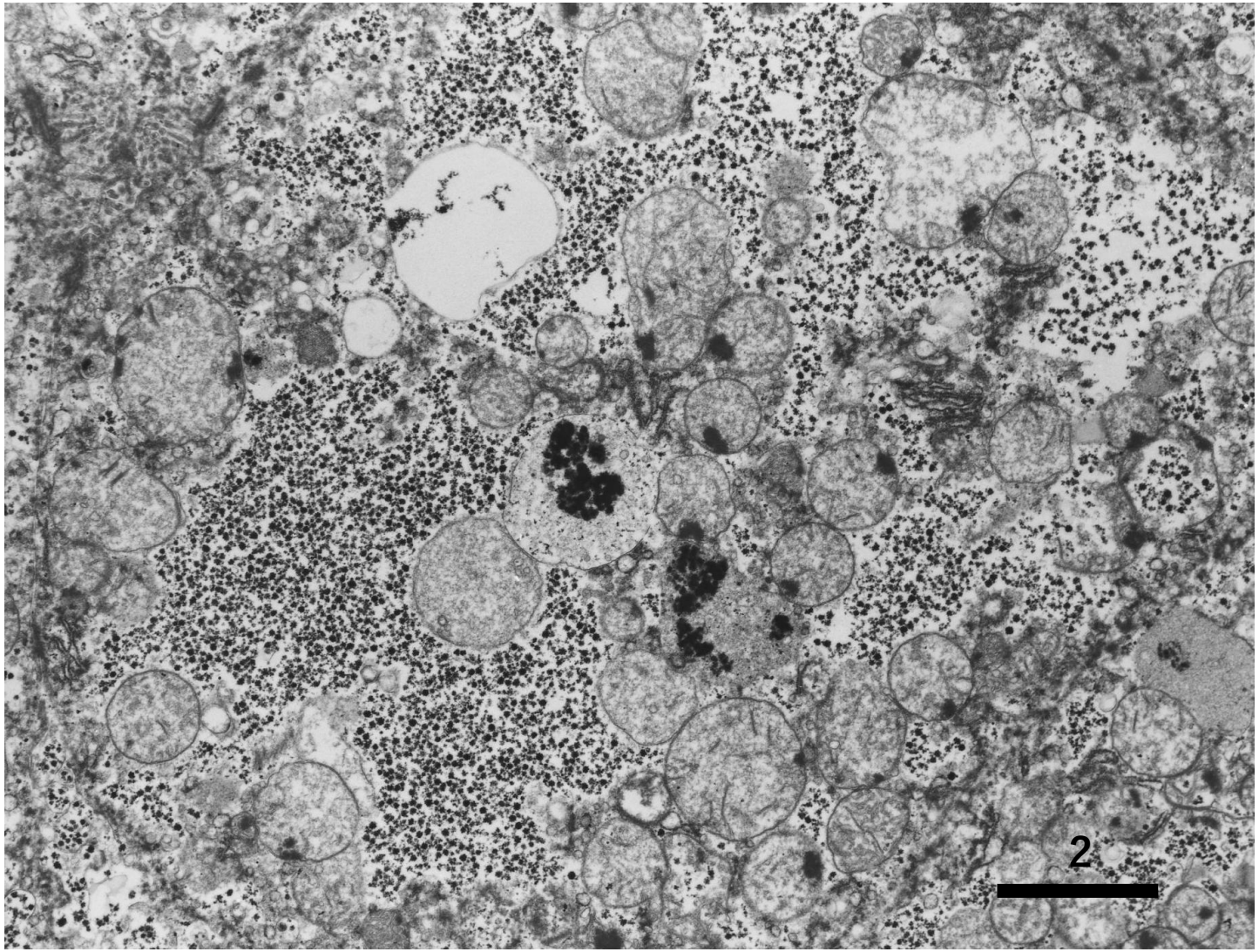
Autopsied liver of an 11-day-old boy with propionic acidemia. The liver is mildly congested. Deposition of fine fat droplets is seen in the hepatocytes (H&E-liver-1).



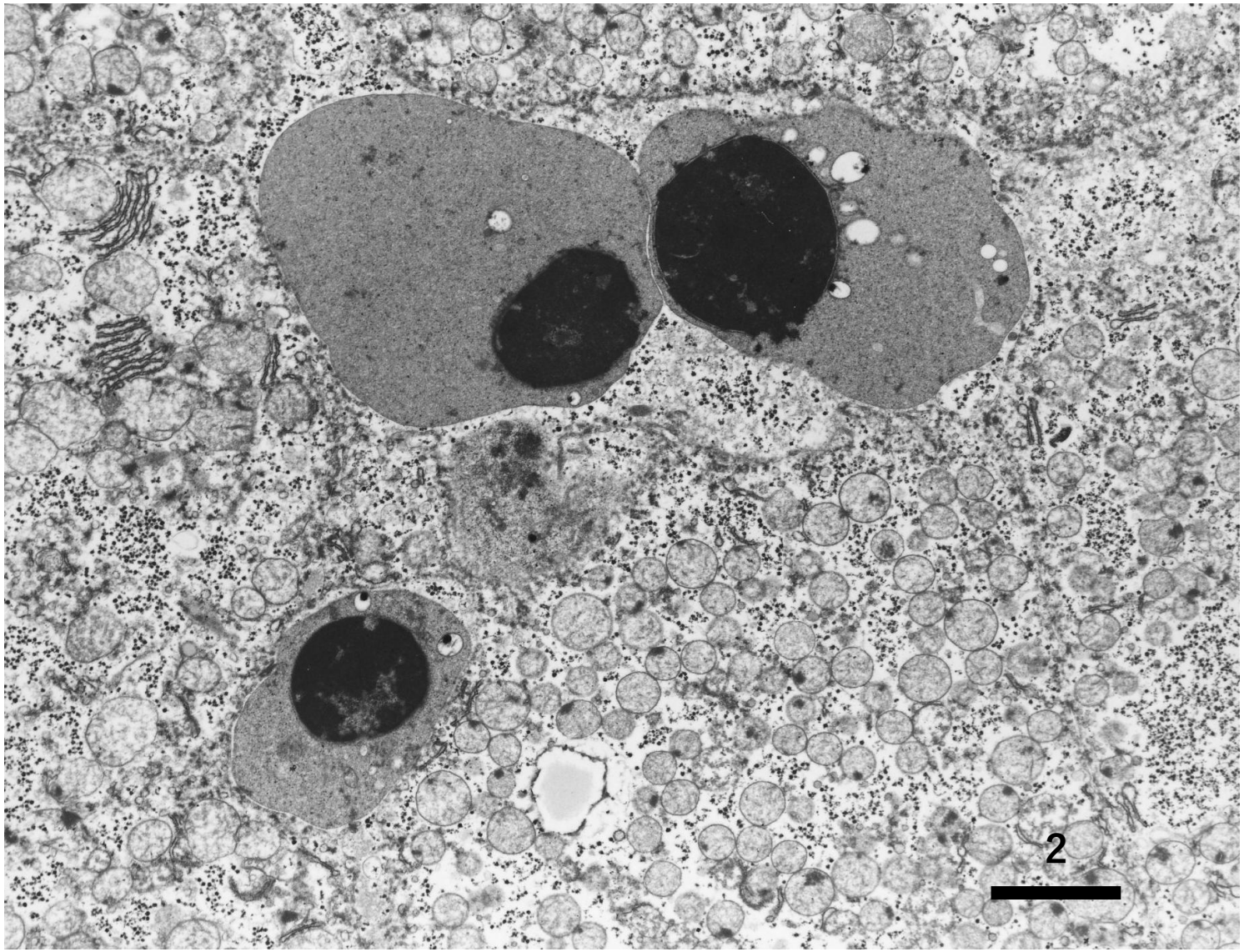
Autopsied liver of an 11-day-old boy with propionic acidemia. The liver is mildly congested. Deposition of fine fat droplets is seen in the hepatocytes (H&E, liver-2).



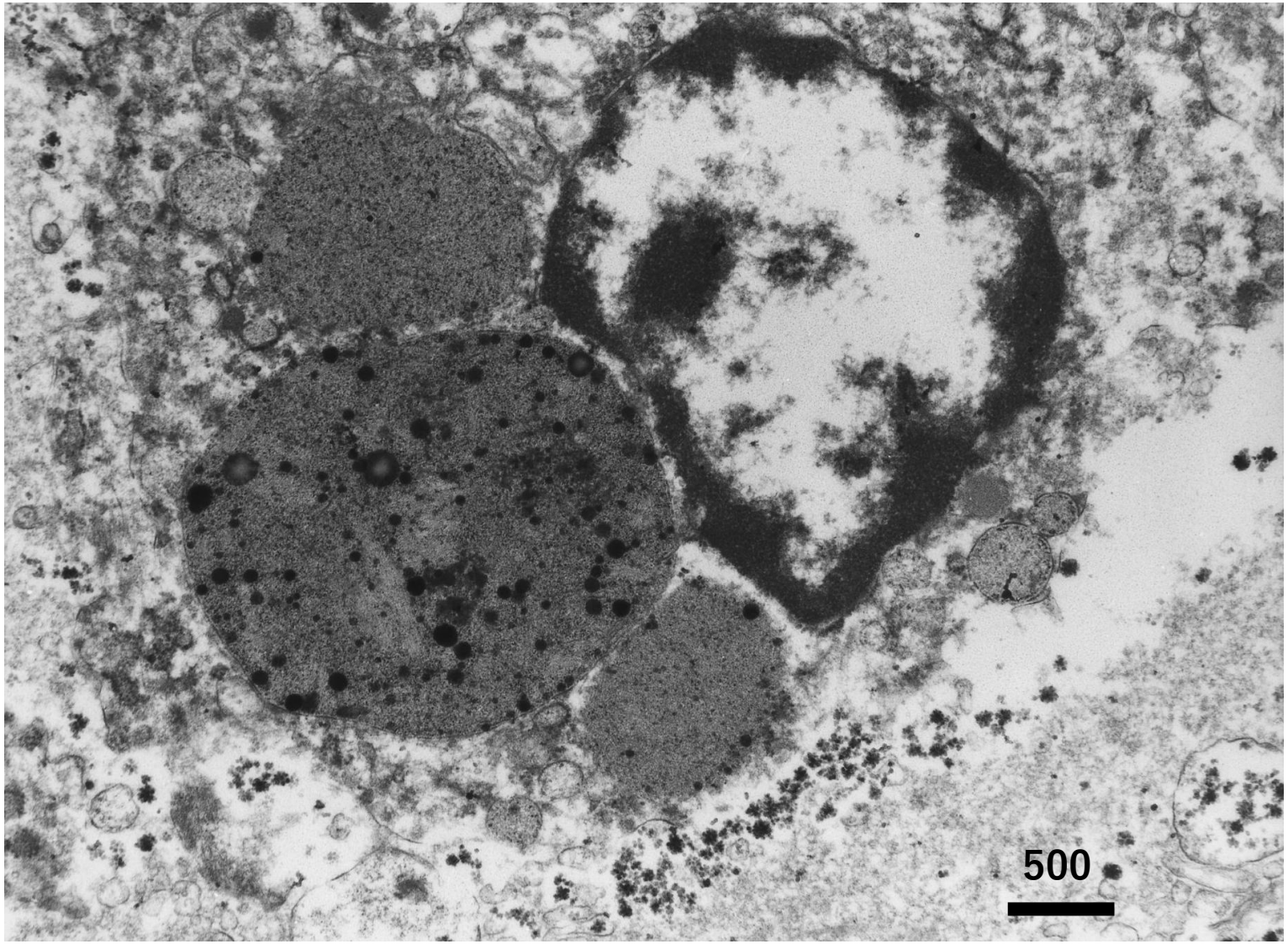
Ultrastructure of the autopsied liver of an 11-day-old boy with propionic acidemia. The hepatocyte contains swollen mitochondria, a fat droplet and an enlarged autophagic vacuole (EM, liver-1).



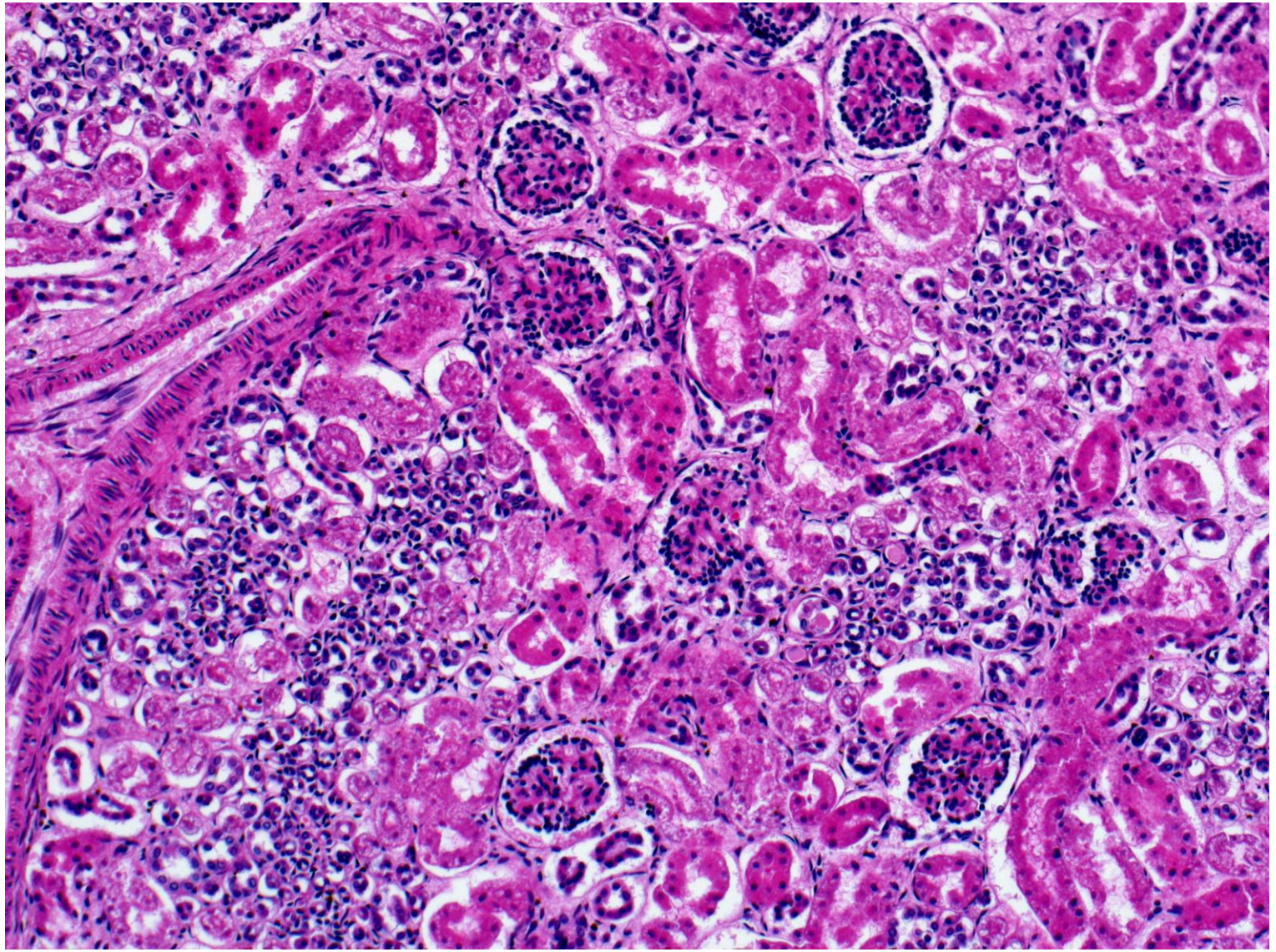
Ultrastructure of the autopsied liver of an 11-day-old boy with propionic acidemia. The hepatocyte contains swollen mitochondria and glycogen particles. The matrix of some mitochondria reveals aggregation of electron-dense substances (dense bodies) (EM, liver-2).



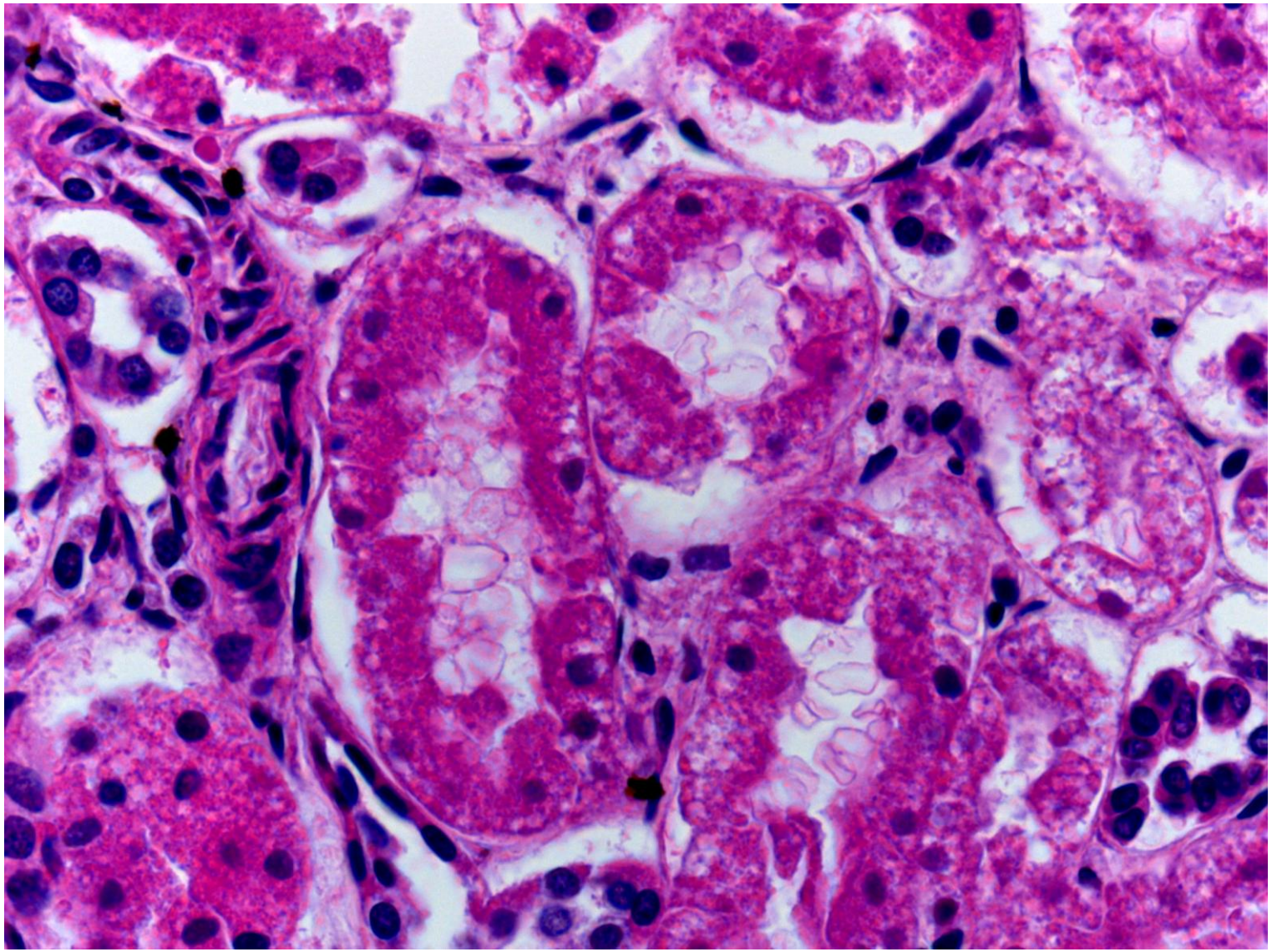
Ultrastructure of the autopsied liver of an 11-day-old boy with propionic acidemia. The hepatocyte contains swollen mitochondria and enlarged autophagic vacuoles with large globular electron-dense bodies (EM, liver-3).



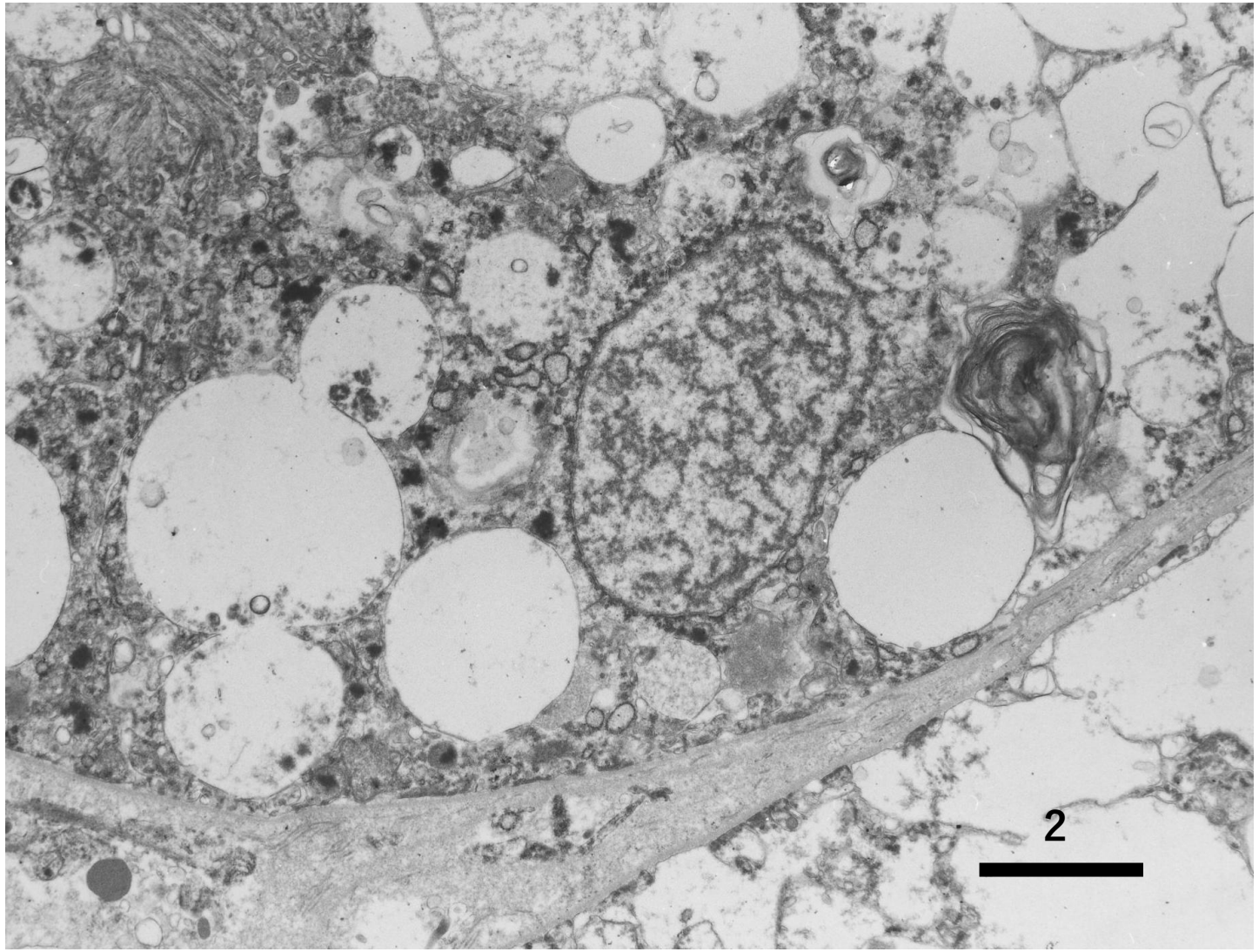
Ultrastructure of the autopsied liver of an 11-day-old boy with propionic acidemia. The hepatocyte contains swollen enlarged autophagic vacuoles with electron-dense granules in the Golgi area (EM, liver-4).



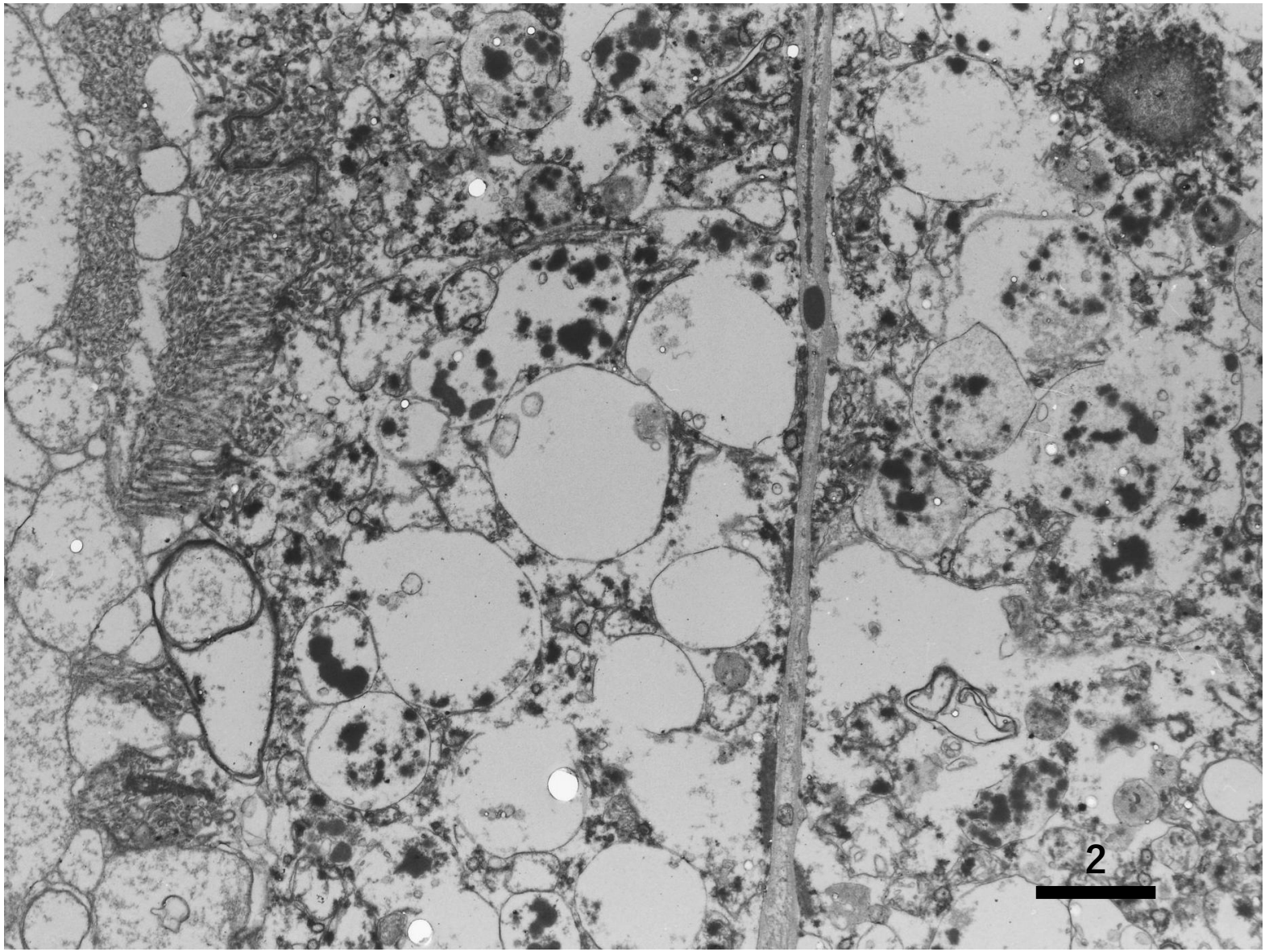
Autopsied kidney of an 11-day-old boy with propionic acidemia. Mild swelling of the proximal renal tubules is seen around the immature glomeruli (H&E, kidney-1).



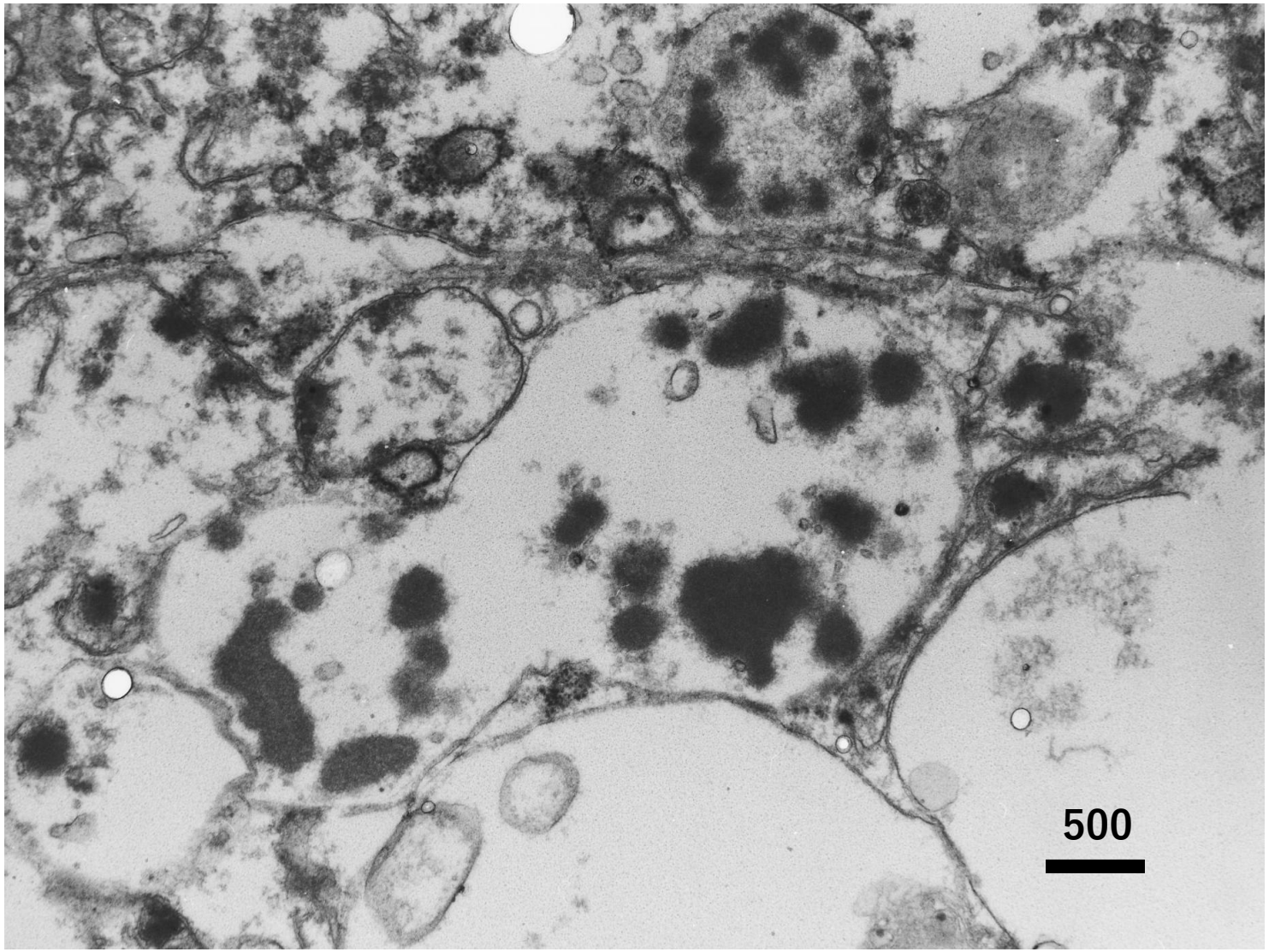
Autopsied kidney of an 11-day-old boy with propionic acidemia. Mild swelling of the proximal renal tubules is seen. Vacuolar change is associated in the eosinophilic cytoplasm (H&E, kidney-2).



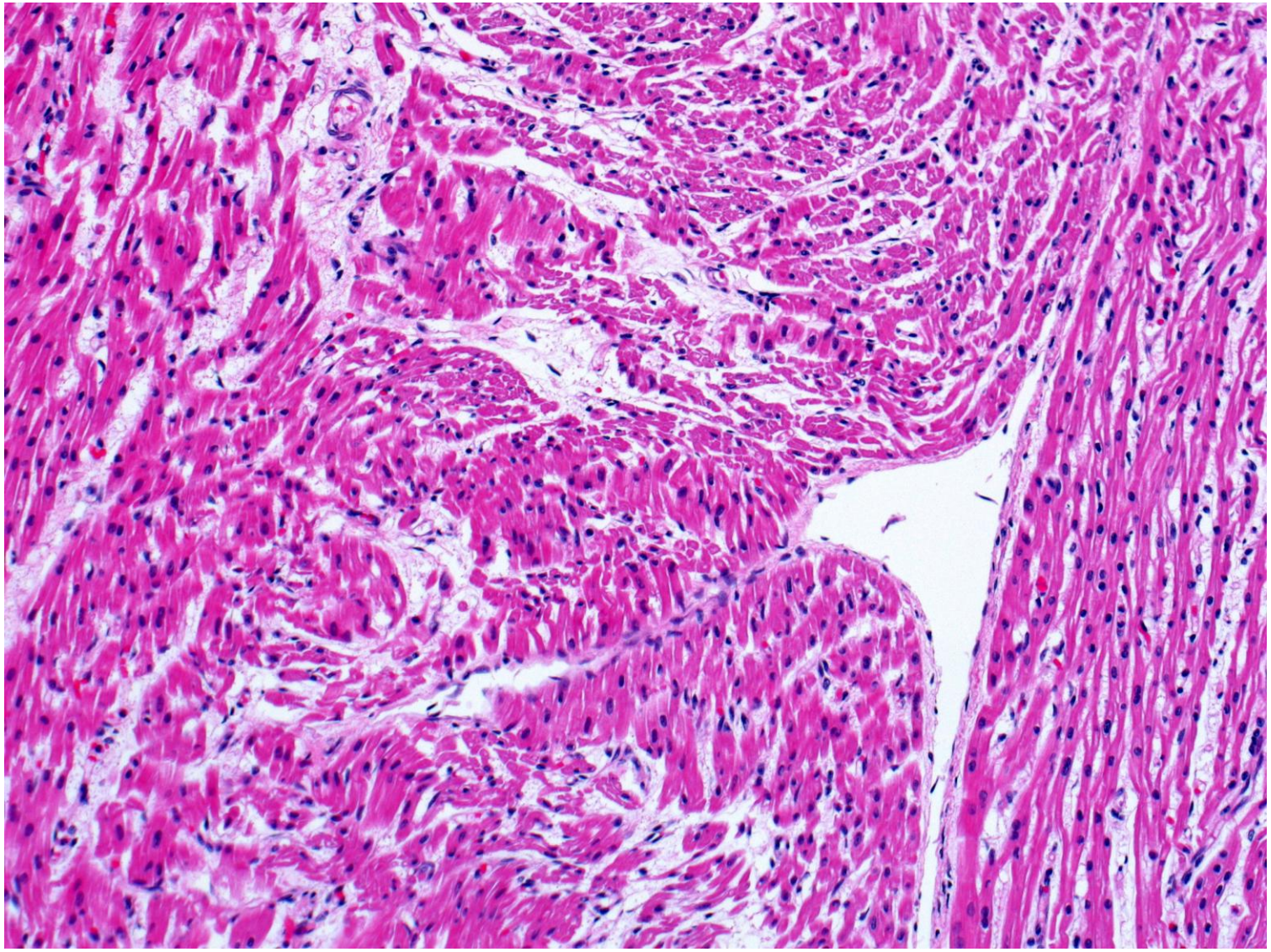
Ultrastructure of the autopsied kidney of an 11-day-old boy with propionic acidemia. The proximal renal tubular epithelial cell contains swollen and vacuolated mitochondria. An autophagic vacuole is also noted (EM, kidney-1).



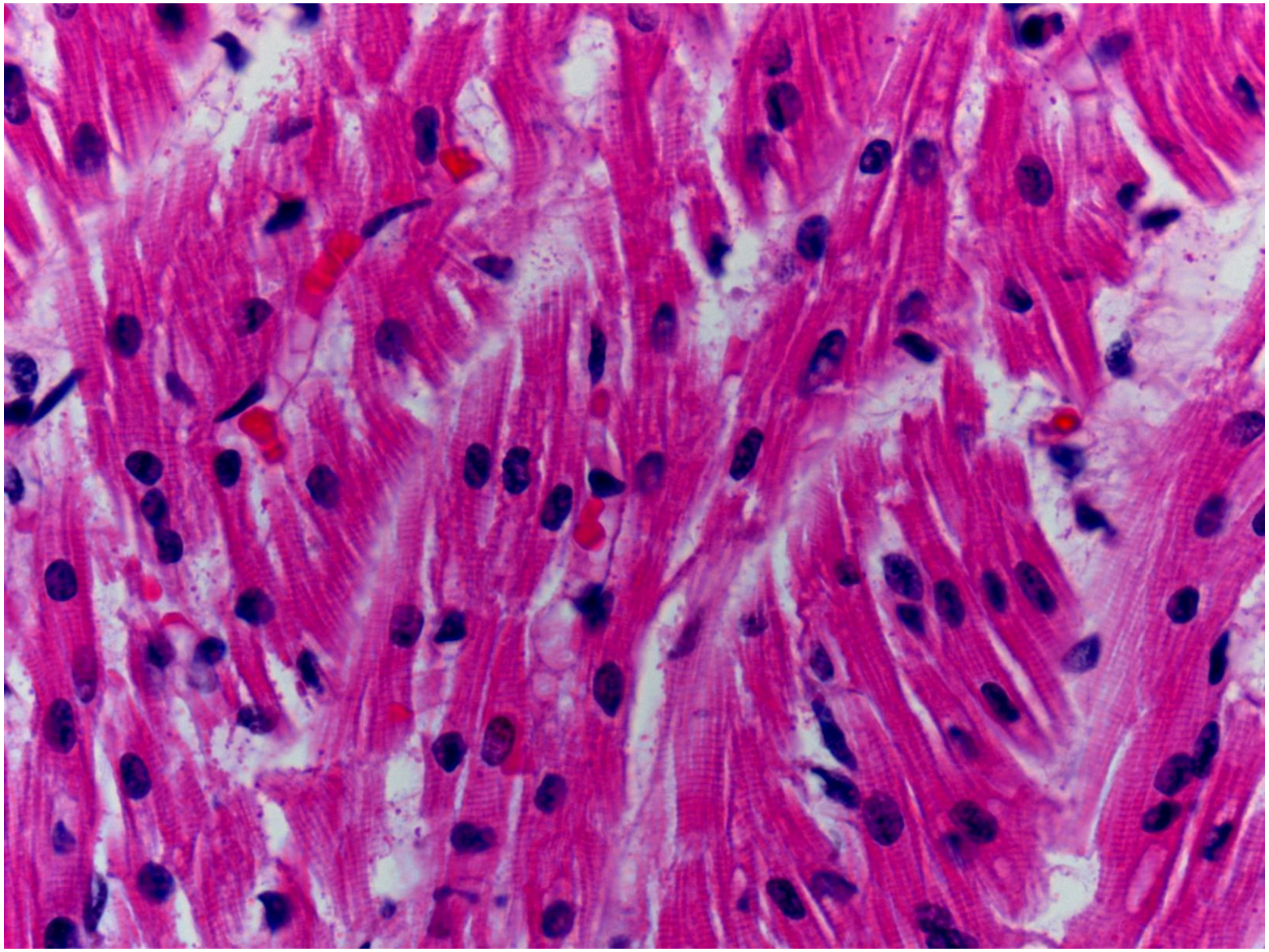
Ultrastructure of the autopsied kidney of an 11-day-old boy with propionic acidemia.
The proximal renal tubular epithelial cell contains swollen and vacuolated mitochondria.
Deposition of electron-dense granules is occasionally observed (EM, kidney-2).



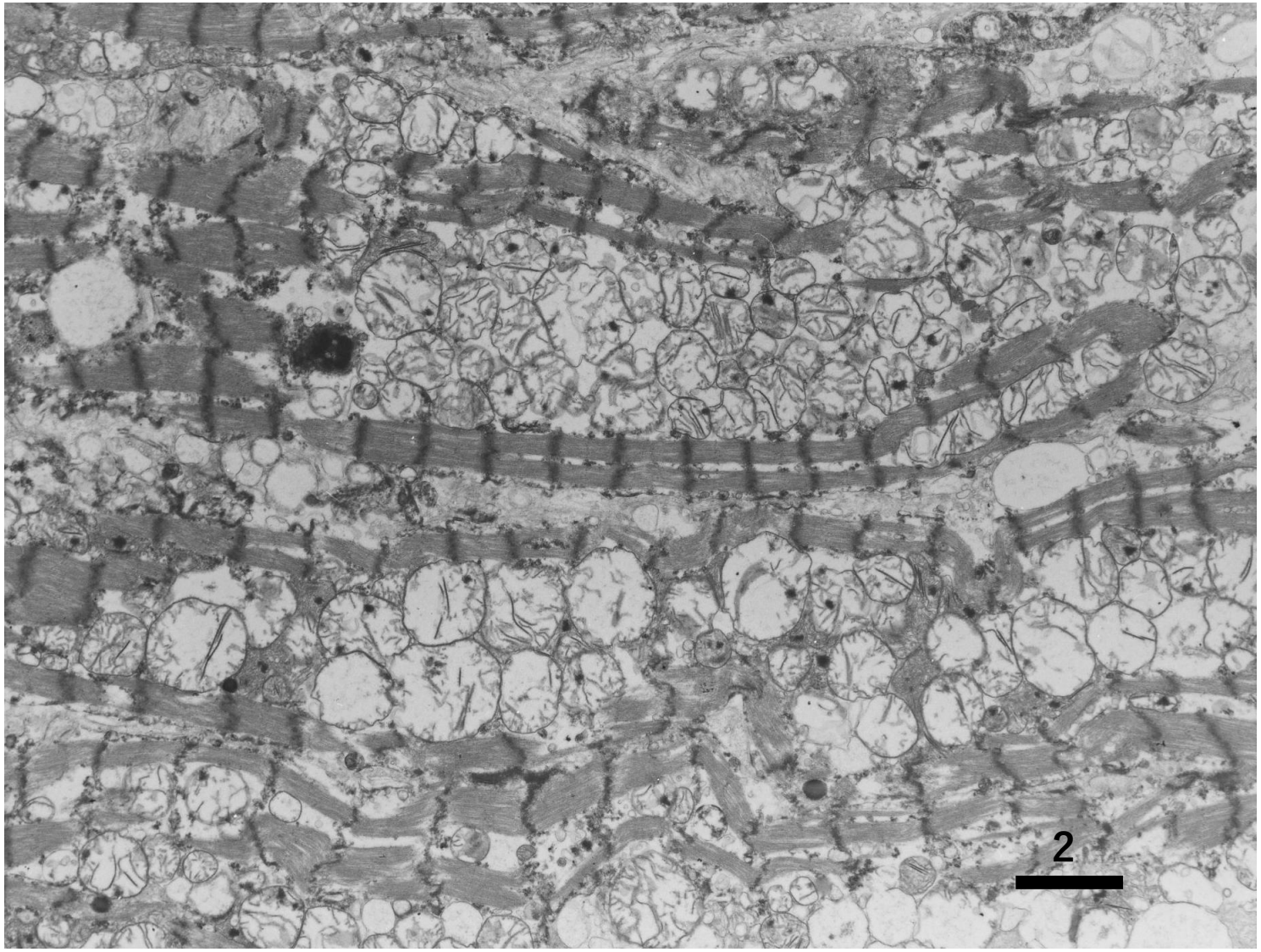
Ultrastructure of the autopsied kidney of an 11-day-old boy with propionic acidemia. The proximal renal tubular epithelial cell contains swollen and vacuolated mitochondria with deposition of electron-dense granules (EM, kidney-3).



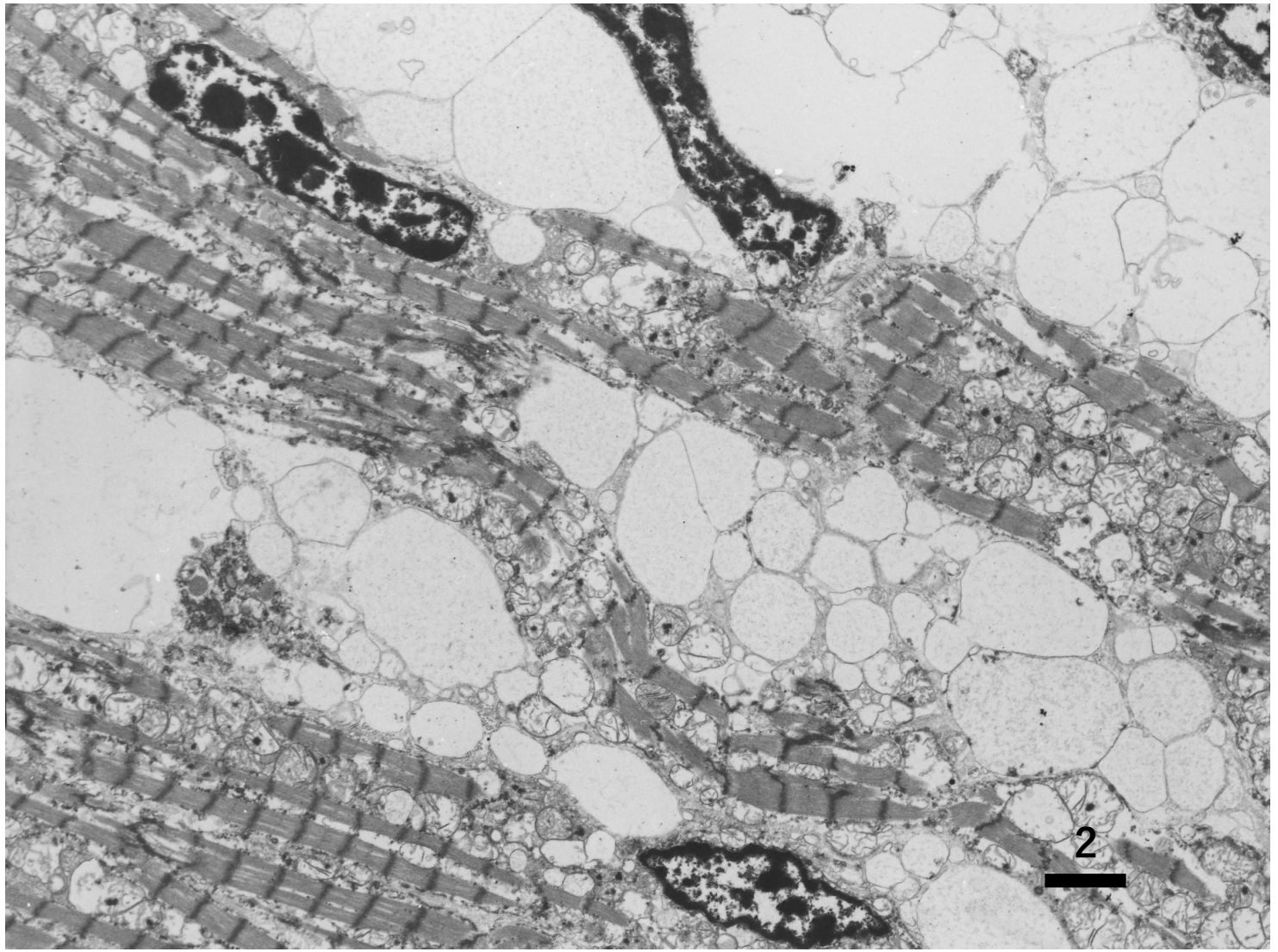
Autopsied heart of an 11-day-old boy with propionic acidemia. No significant change is discerned light microscopically (H&E, heart-1).



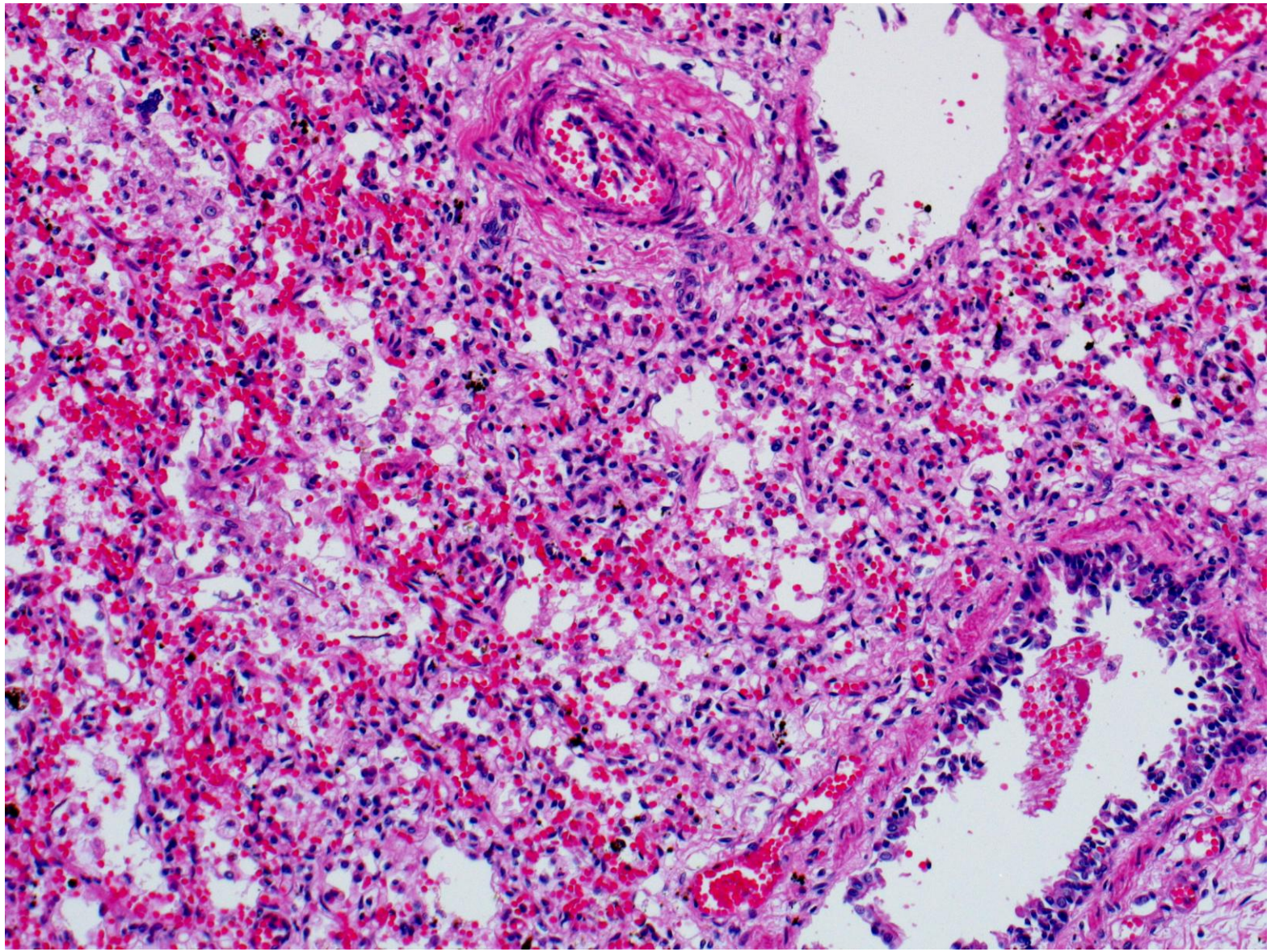
Autopsied heart of an 11-day-old boy with propionic acidemia. No significant change is discerned light microscopically. A few vacuoles are seen in the cytoplasm of cardiomyocytes (H&E, heart-2).



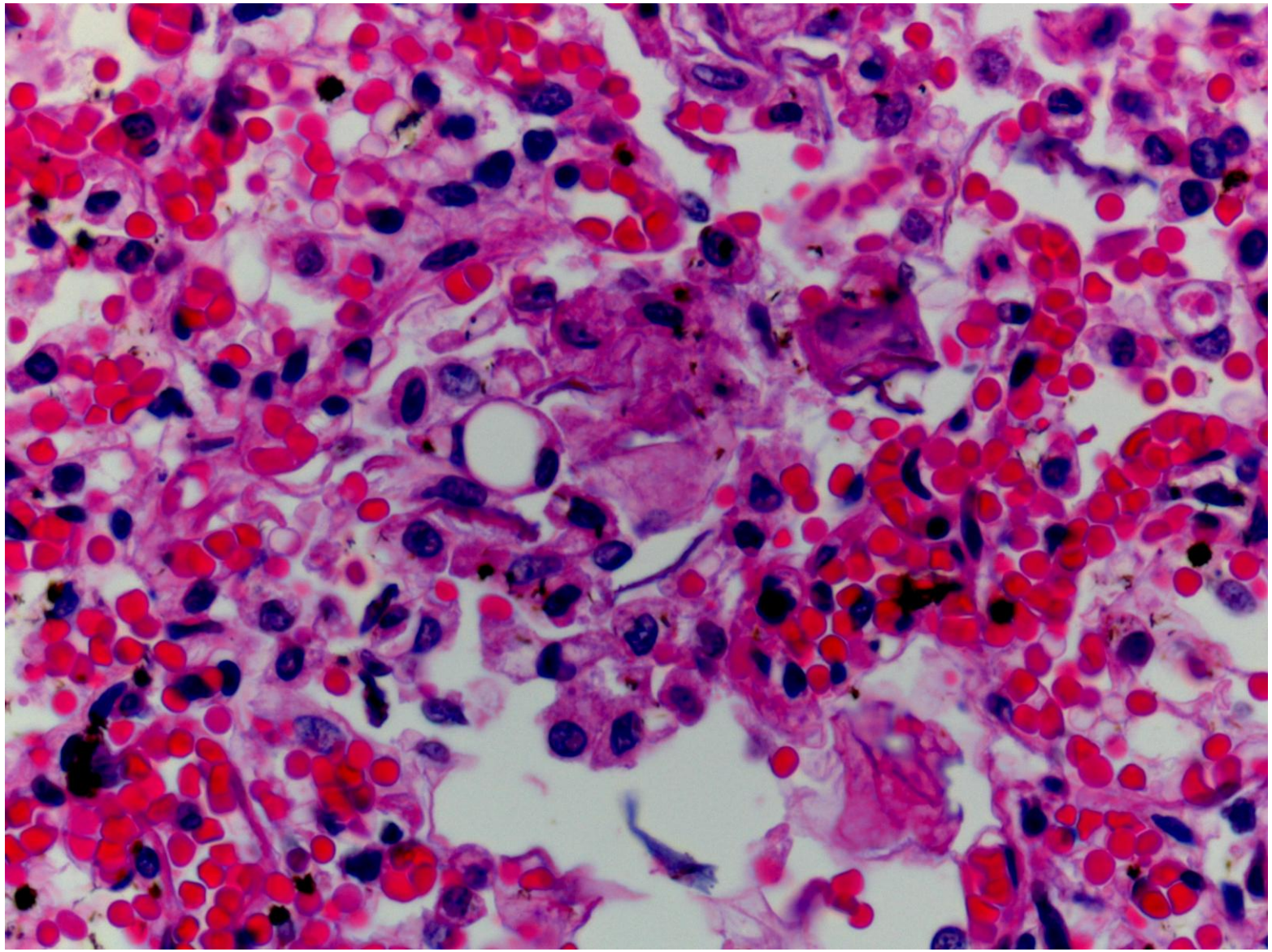
Ultrastructure of the autopsied heart of an 11-day-old boy with propionic acidemia. The cardiomyocyte contains clusters of swollen mitochondria. Some mitochondria reveals vacuolar change (EM, heart-1).



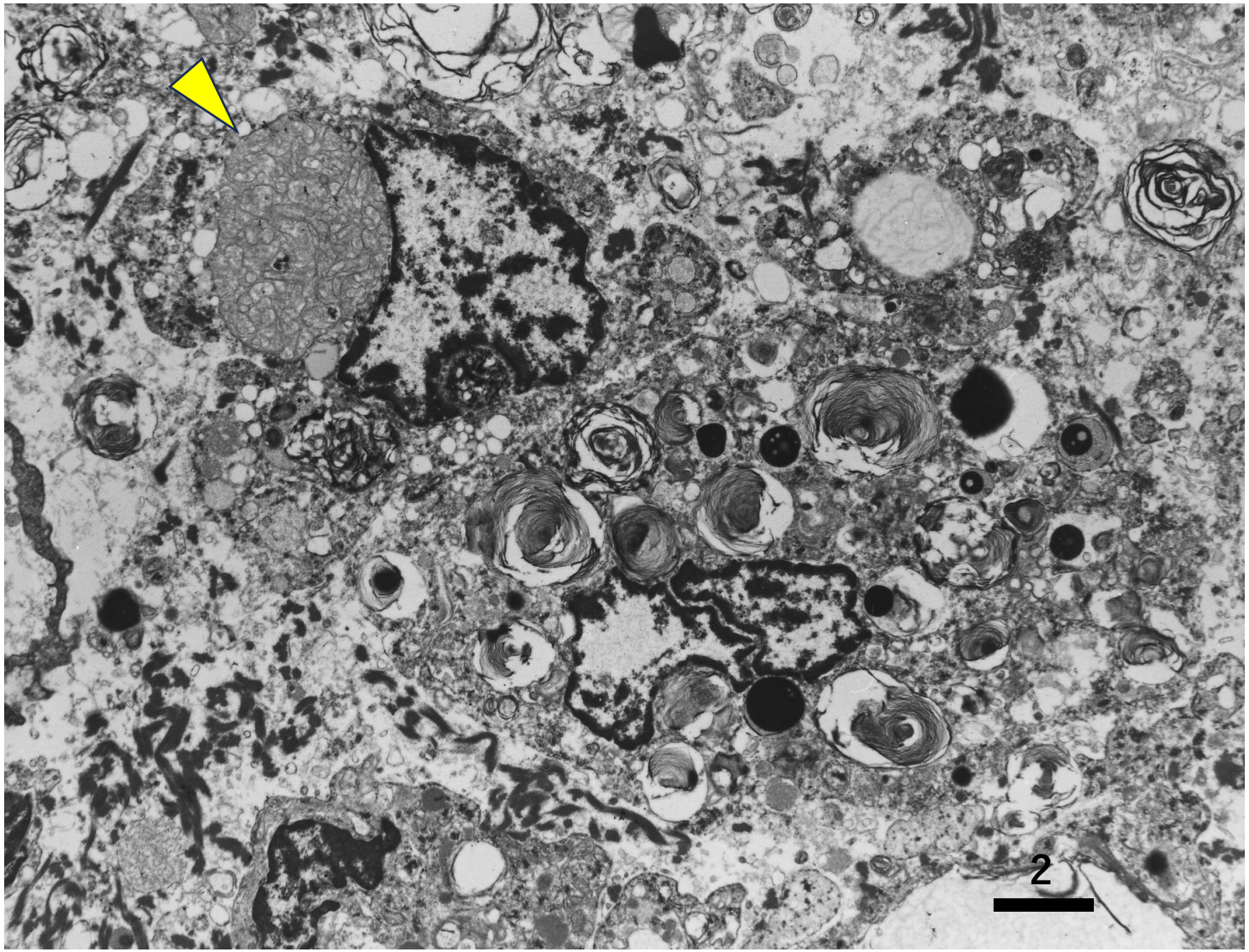
Ultrastructure of the autopsied heart of an 11-day-old boy with propionic acidemia. In this area, the cardiomyocyte contains clusters of swollen and vacuolated mitochondria (EM, heart-2).



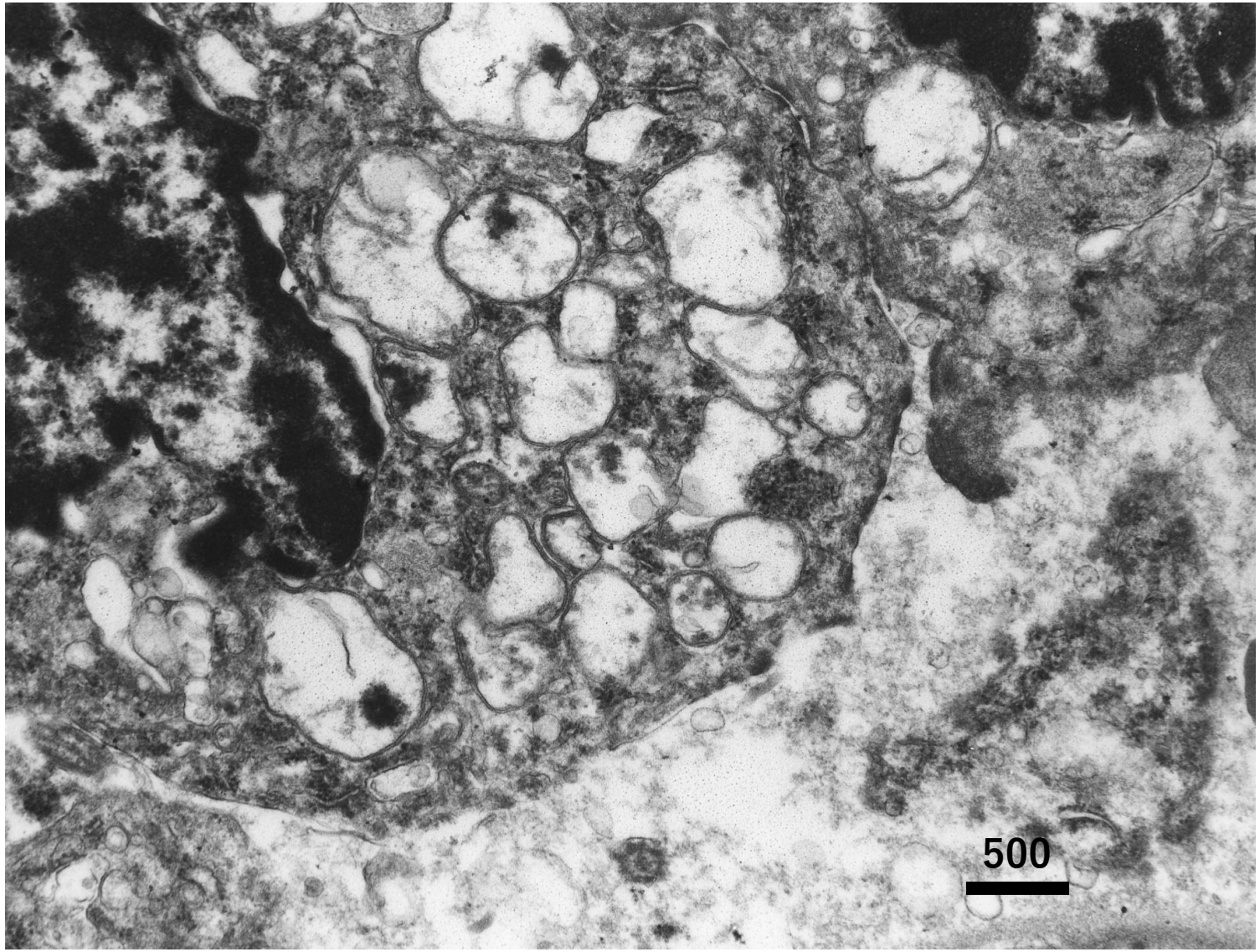
Autopsied lung of an 11-day-old boy with propionic acidemia.
Congestive change is discerned (H&E, lung-1).



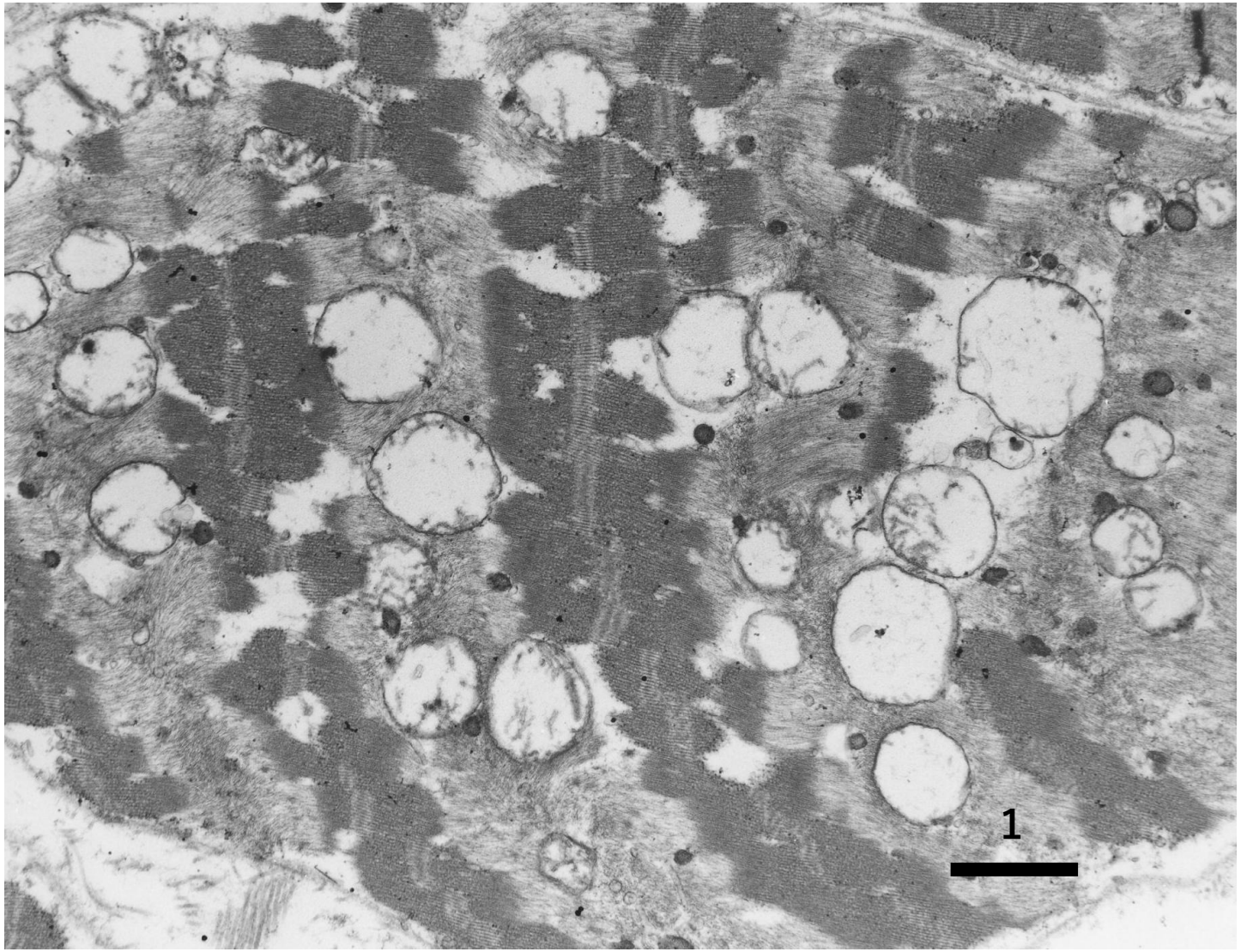
Autopsied lung of an 11-day-old boy with propionic acidemia. The congestive change is associated with mild swelling of the type II pneumocytes (H&E, lung-2).



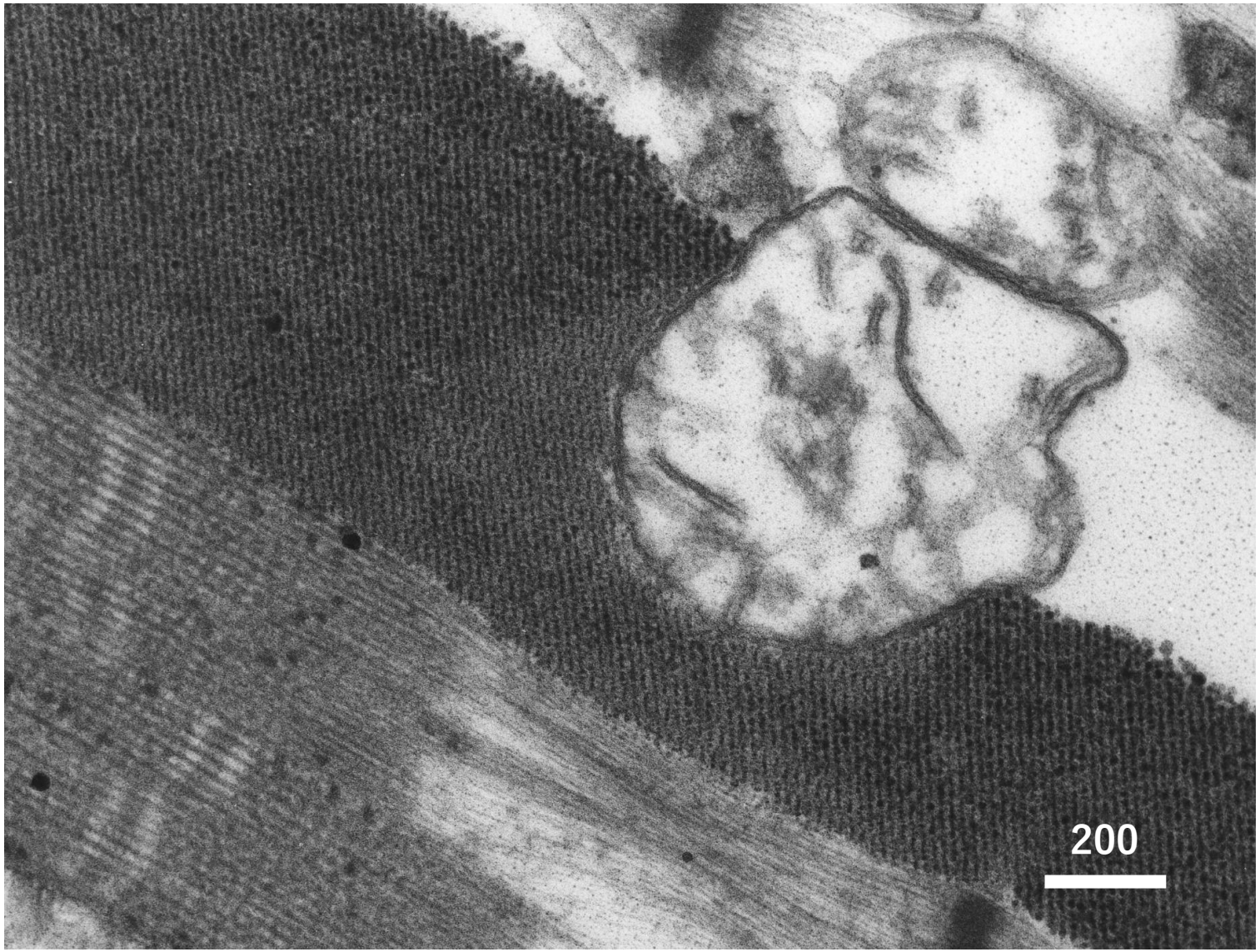
Ultrastructure of the autopsied lung of an 11-day-old boy with propionic acidemia. The type II pneumocytes contain lamellar inclusion bodies and swollen mitochondria. An autophagic vacuole is seen in the Golgi area (arrowhead) (EM, lung-1).



Ultrastructure of the autopsied lung of an 11-day-old boy with propionic acidemia. The type II pneumocytes contain swollen and vacuolated mitochondria. Dot-like dense bodies representing mitochondrial DNA are scattered (EM, lung-2).



Ultrastructure of the autopsied striated muscle of an 11-day-old boy with propionic acidemia. The striated muscle cell contains swollen and vacuolated mitochondria (EM, muscle-1).



Ultrastructure of the autopsied striated muscle of an 11-day-old boy with propionic acidemia. The striated muscle cell contains swollen mitochondria and crystalline change of myofibrillar component (EM, muscle-2).