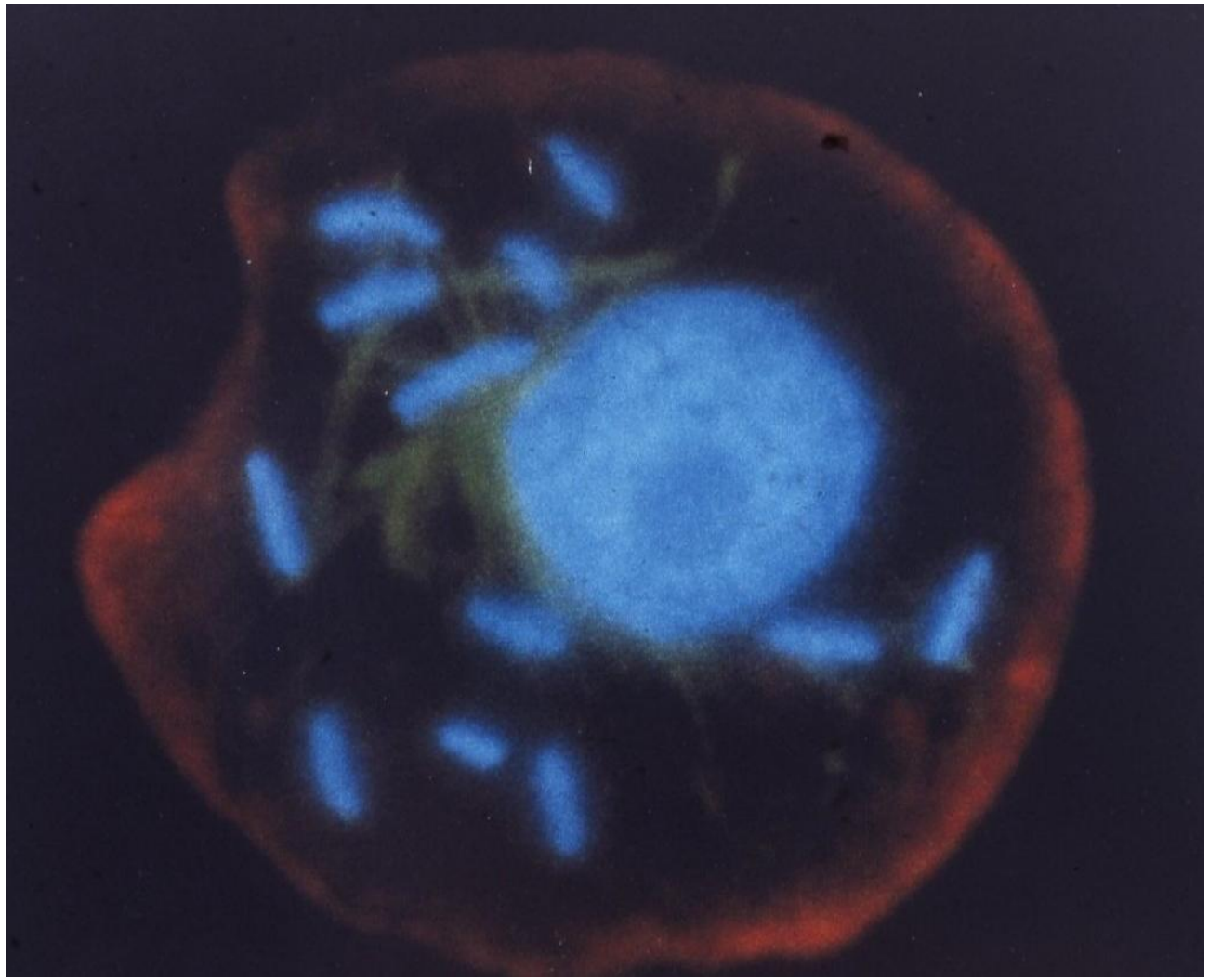
Pathology of mitochondria

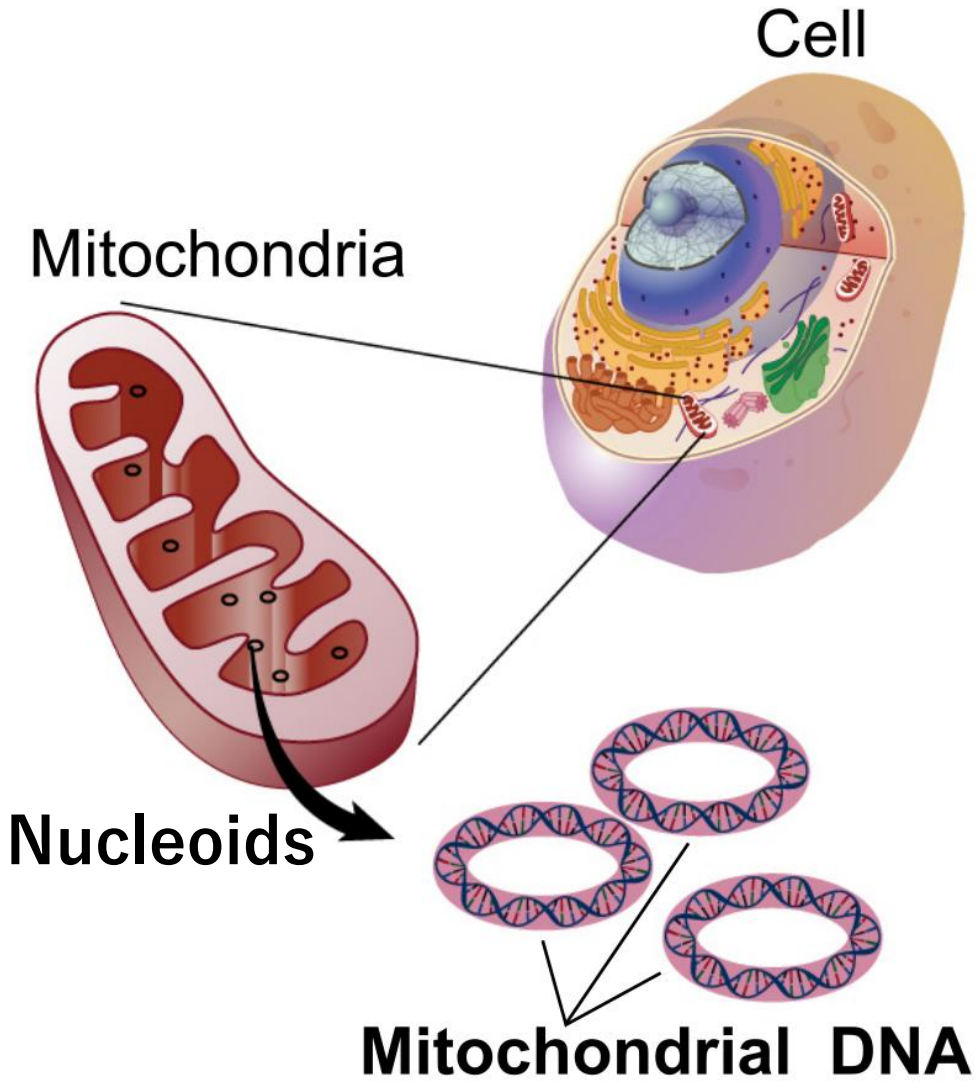
Mitochondria, the powerhouse organelle of the cell, are able to adjust and respond to different stressors and metabolic needs within a cell, showcasing their plasticity and dynamic nature. Mitochondrial dynamics refers to the changing process of fission, fusion, mitophagy and transport, crucial for the optimal function in signal transduction and metabolism. An imbalance in mitochondrial dynamics can disrupt mitochondrial function, leading to abnormal cellular fate, and a range of diseases, including neurodegenerative disorders, metabolic diseases, cardiovascular diseases and neoplasms. Mitochondria are of maternal origin and possess circular DNA concentrated in the nucleoid in the matrix. Mitochondrial proteins are partly synthesized from the mitochondrial DNA, but many are transported from the cytoplasm, labeled with transmembrane signals (leading peptide). Mitochondria are rich in heme-containing cytochrome P450, giving the red/brown color to the cells. A variety of fine morphological changes, including giant mitochondria and crystalline change of the cristae, particularly in the hepatocytes, are seen under various conditions. Oncocytoma (mitochondrioma) is characterized by the tumor cells rich in mitochondria. Mitochondriopathy is a congenital condition with abnormal mitochondrial function and mitochondrial fine morphology. Reye syndrome, acute encephalopathy with fine droplet fatty change in the liver caused by acute mitochondrial insufficiency, is provoked by the intake of antipyretics, particularly aspirin in children. Among single-celled obligate anaerobic parasites, *Entamoeba histolytica* lacks mitochondria, while *Blastocystis hominis* has mitochondria. The function of mitochondria in the mysterious microbe *B. hominis* should be established.

Ref.: Chen W, et al. Mitochondrial dynamics in health and disease: mechanisms and potential targets. Sig Transduct Target Ther 2023; 8: 333. doi: 10.1038/s41392-023-01547-9

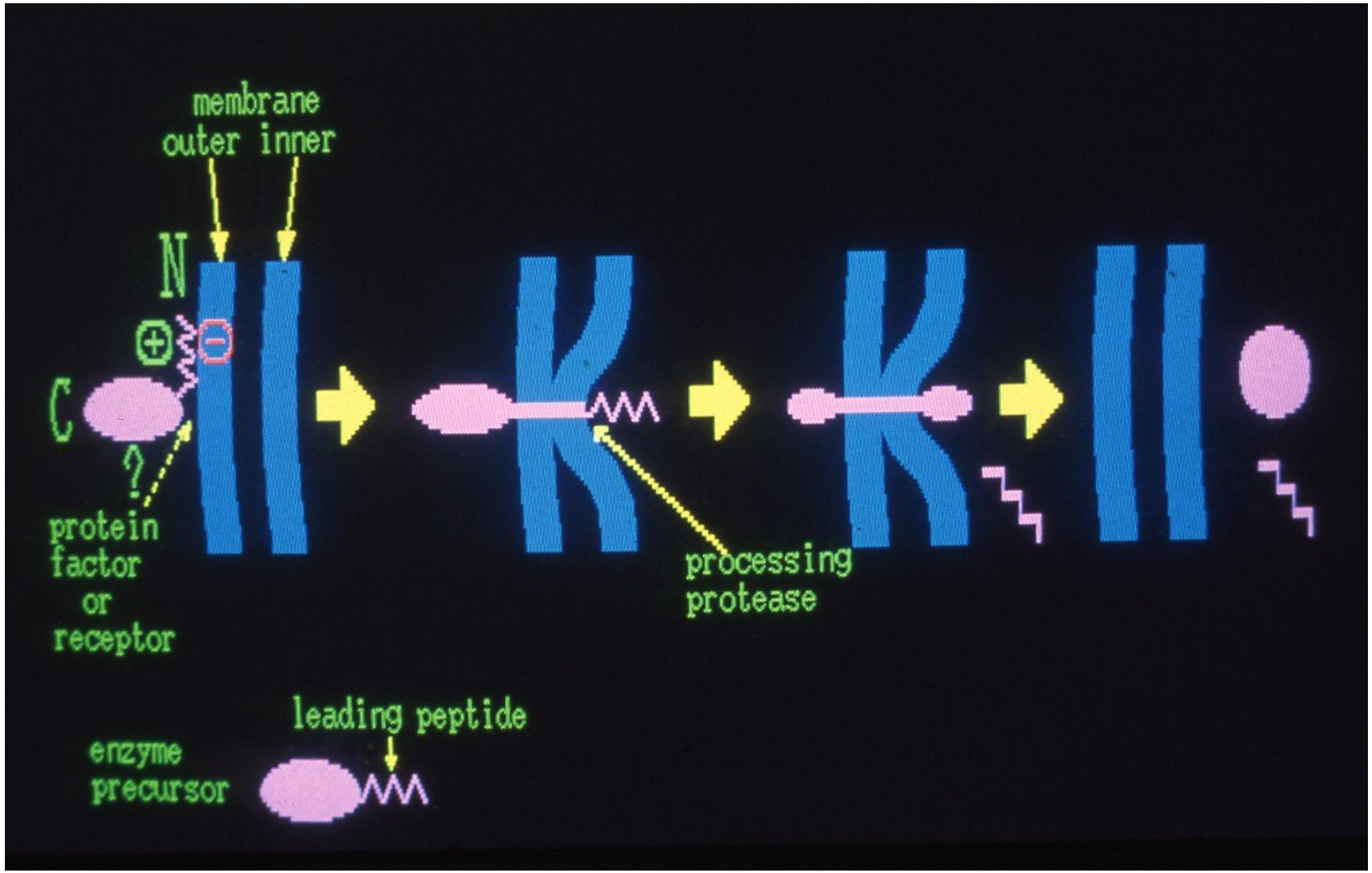
Cyanobacterium is the oldest life form on the earth. They existed billions of years ago in the early extreme environments before plants and animals emerged. Mitochondria emerged through an endosymbiotic event involving a proteobacterium (cyanobacterium) and an archaeal host.



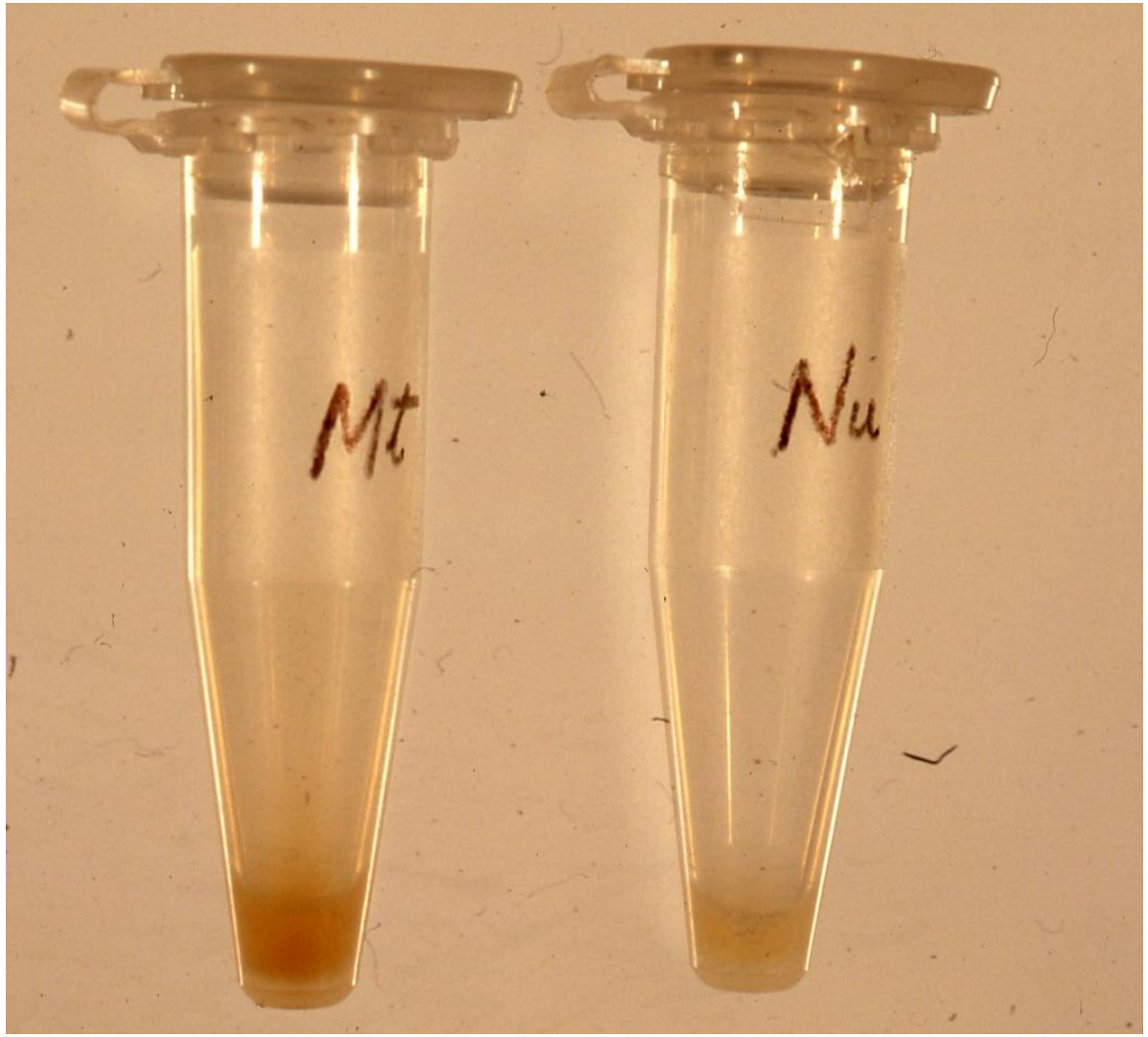
An amebic form of cellular slime molds. Triple immunofluorescence study for localizing DNA (blue), microtubule (green) and actin (red). DNA is located not only in the nucleus but also in mitochondria. Microtubules are clustered adjacent to the nucleus. Actin is localized at the periphery of the cell.



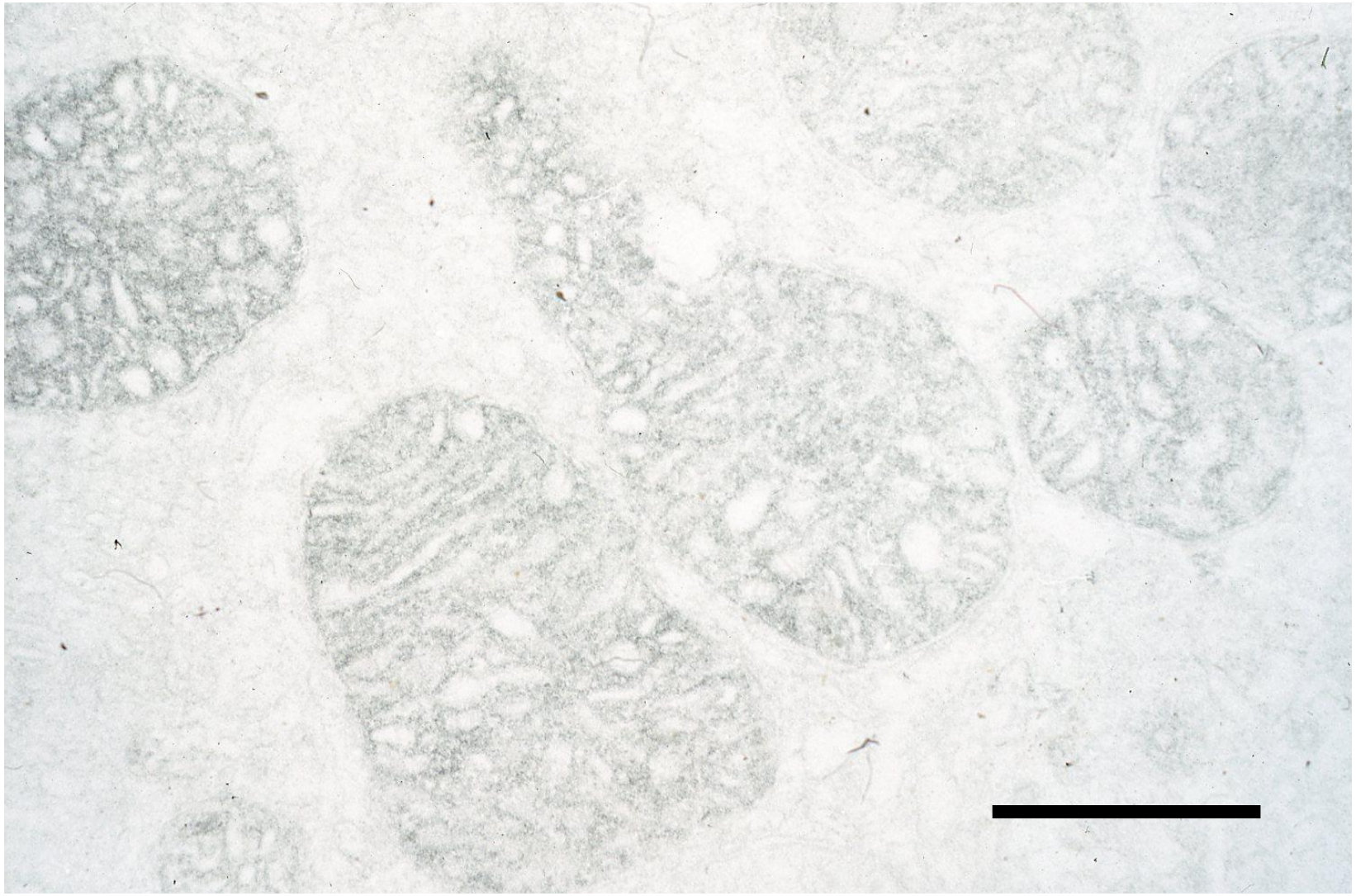
Mitochondrial DNA is seen as a small circular structure (circular DNA), identical to bacterial cells, inside mitochondria, the powerhouse of the cell. The mitochondria and mitochondrial DNA are passed exclusively from mother to offspring through the egg cell. Mitochondria of the sperm can not enter the fertilized egg. Borrowed from Wikipedia (Mitochondrial DNA).



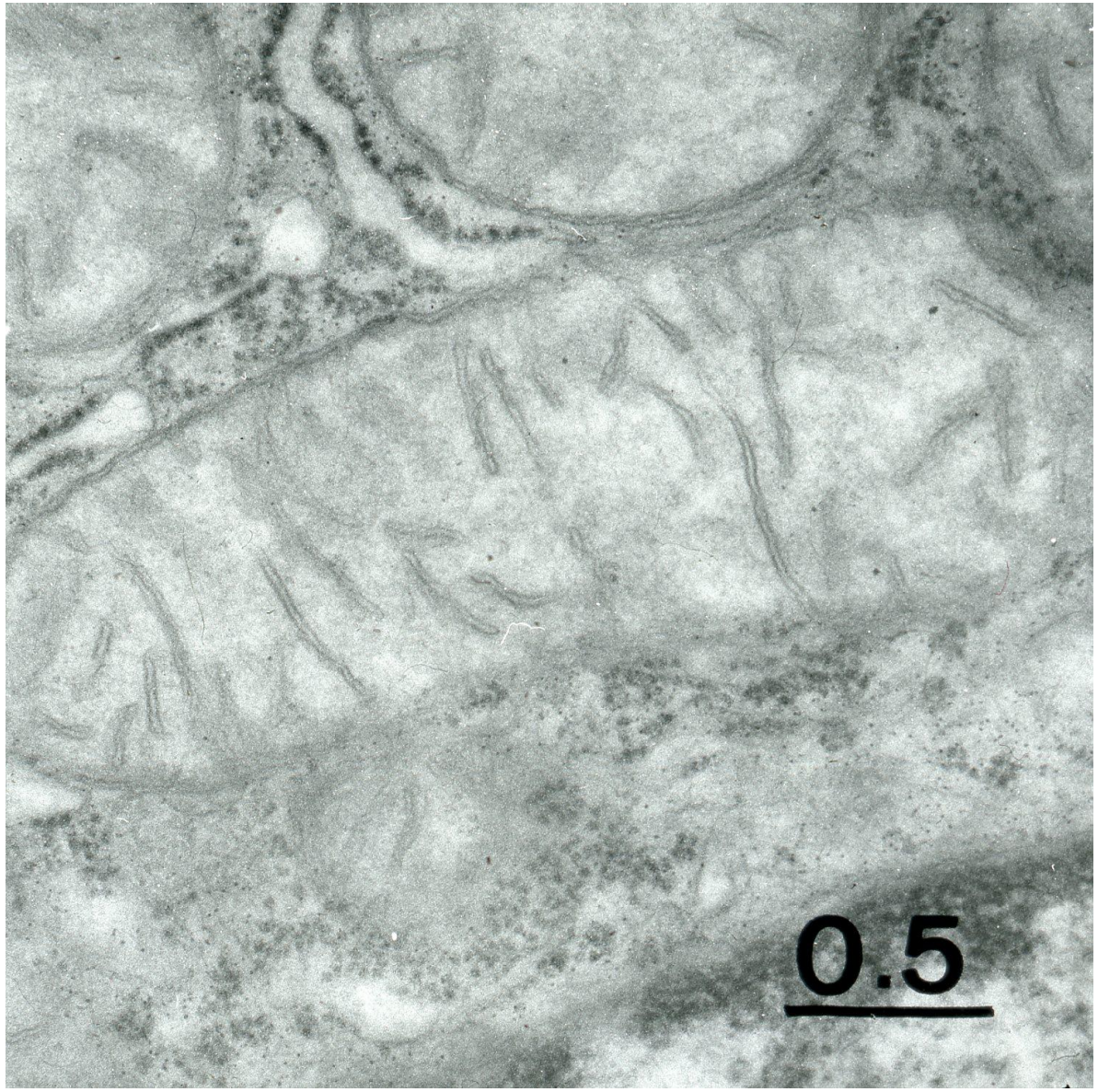
Schematic representation of the transmembrane transport of mitochondrial proteins encoded by nuclear DNA. The “leading peptide” functions as the mitochondrial transportation signal. The mature mitochondrial protein is a little bit shorter than the precursor protein.



The color of ultracentrifuged mitochondrial (Mt) and nuclear (Nu) fractions of the normal rat brain. Note the red/brown color of the mitochondrial fraction, indicating the presence of heme protein (cytochrome).

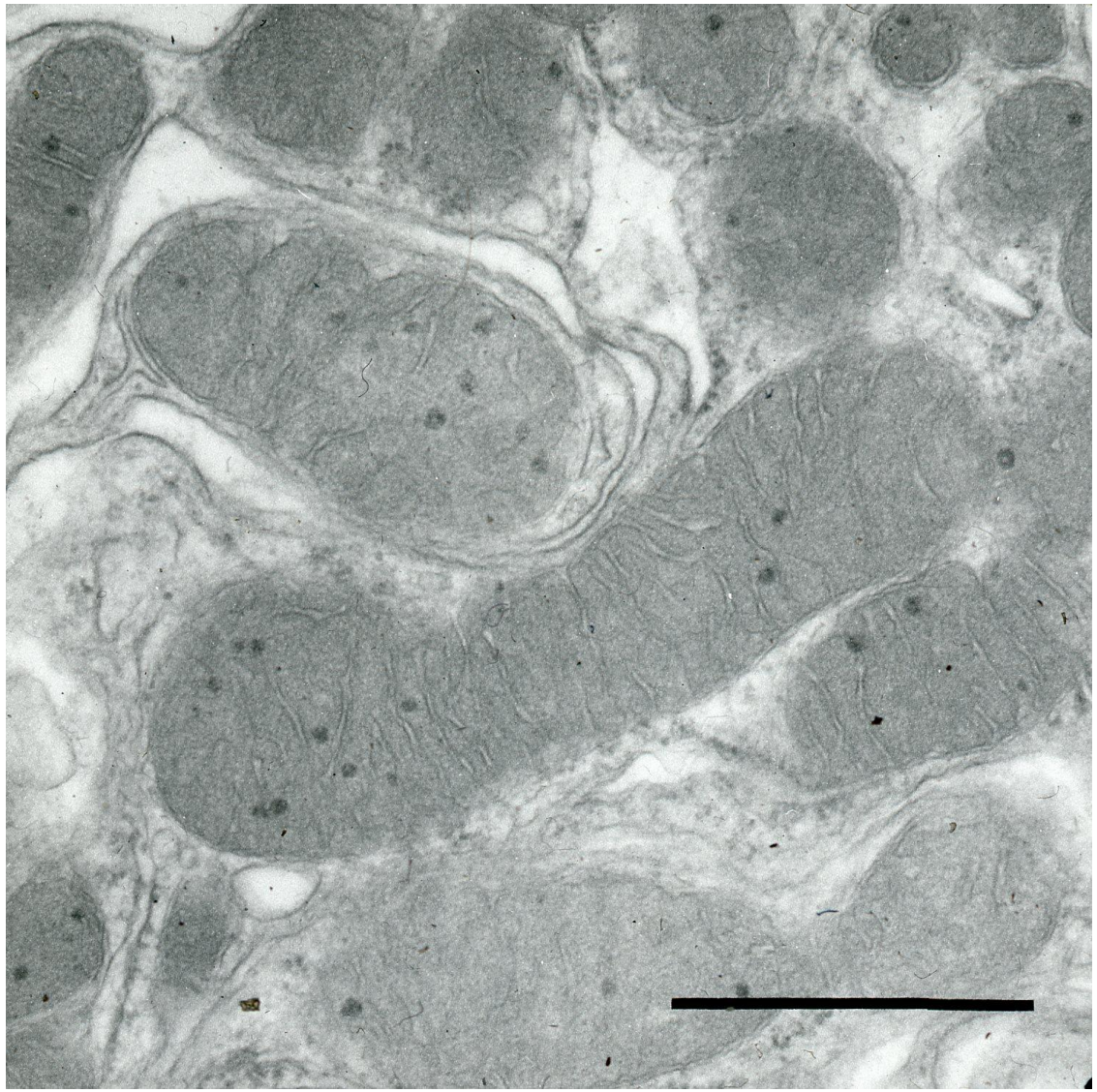


Pre-embedding immunoelectron microscopic demonstration of cytochrome P450 in mitochondria in the rat hepatocyte. P450, a Fe-containing heme protein, is localized along the cristae. HRP-labeled Fab fragment of IgG against rat P450 was used for study.



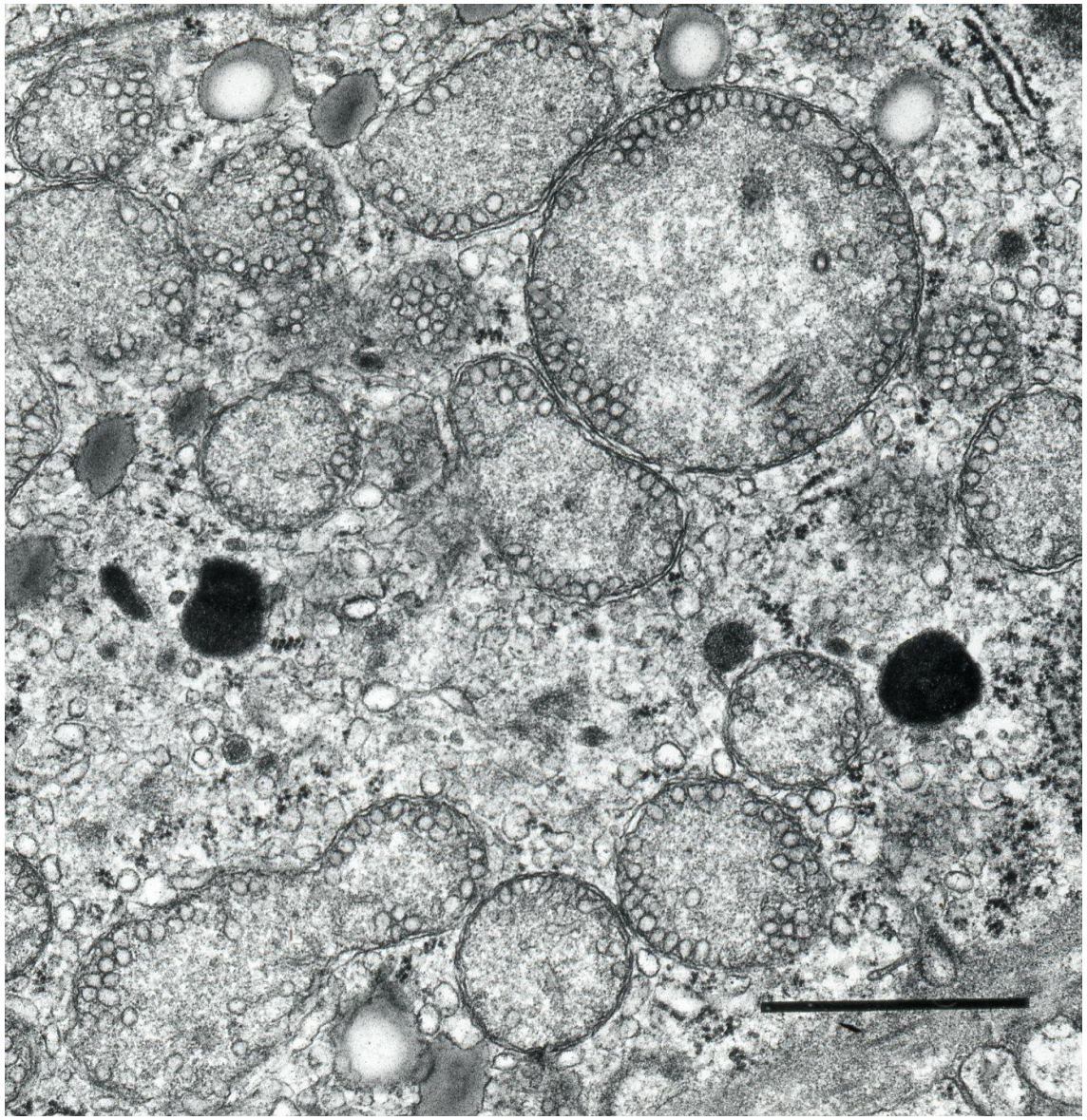
Mitochondria in a normal human hepatocyte. Double-contoured membranes and cristae are observed. The cristae are continuous to the inner part of the double mitochondrial membrane.

Mitochondrial division in an amebic form of the cellular slime mold. Mitochondrial DNA is also duplicated.

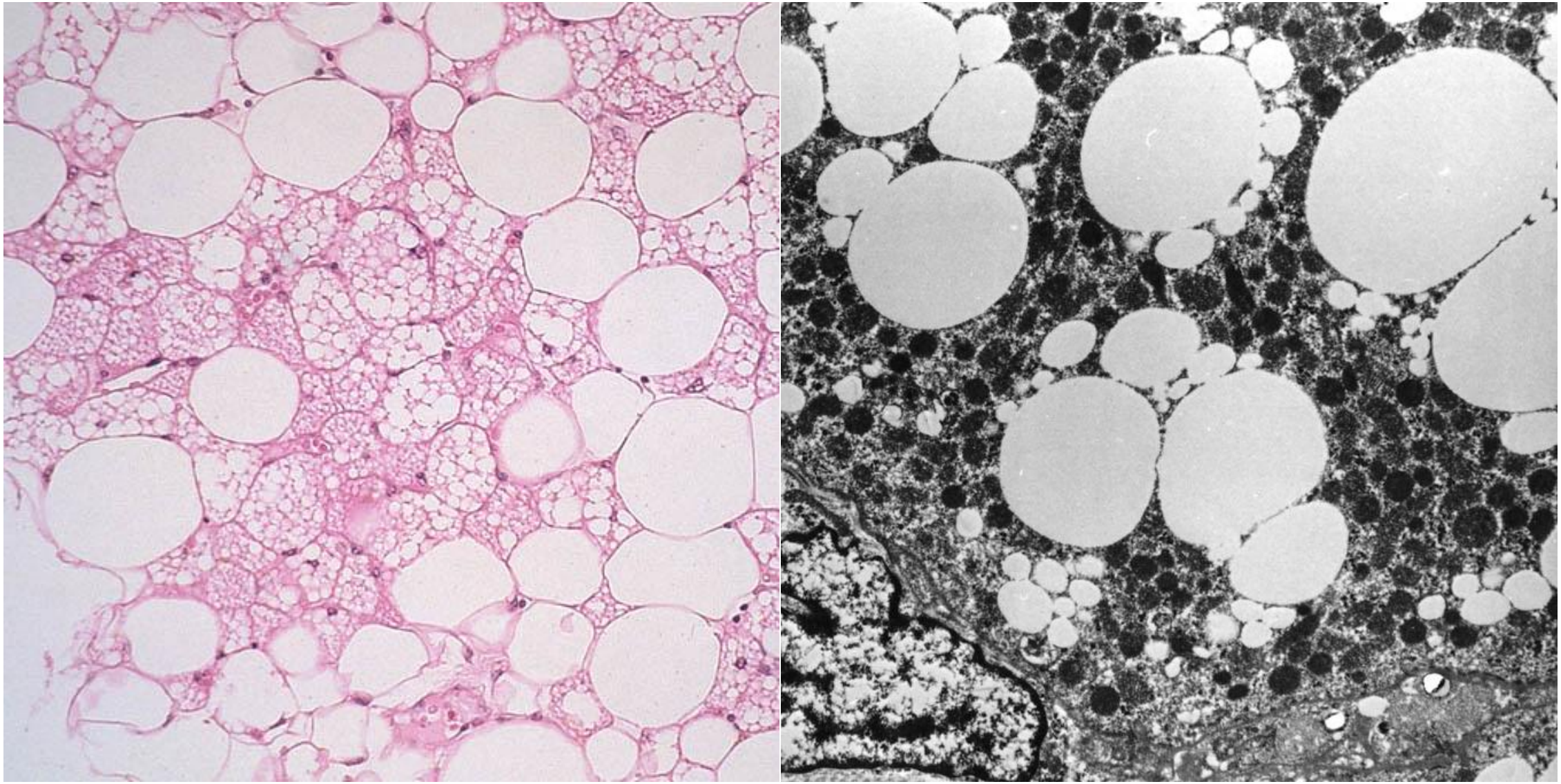


Mitochondria in the epithelial cell of the proximal renal tubule. Dot-like electron-dense granules represent mitochondrial DNA, and are called nucleoids. Note that smooth endoplasmic reticula surround the mitochondria, indicating the interaction between the smooth endoplasmic reticulum and mitochondria.

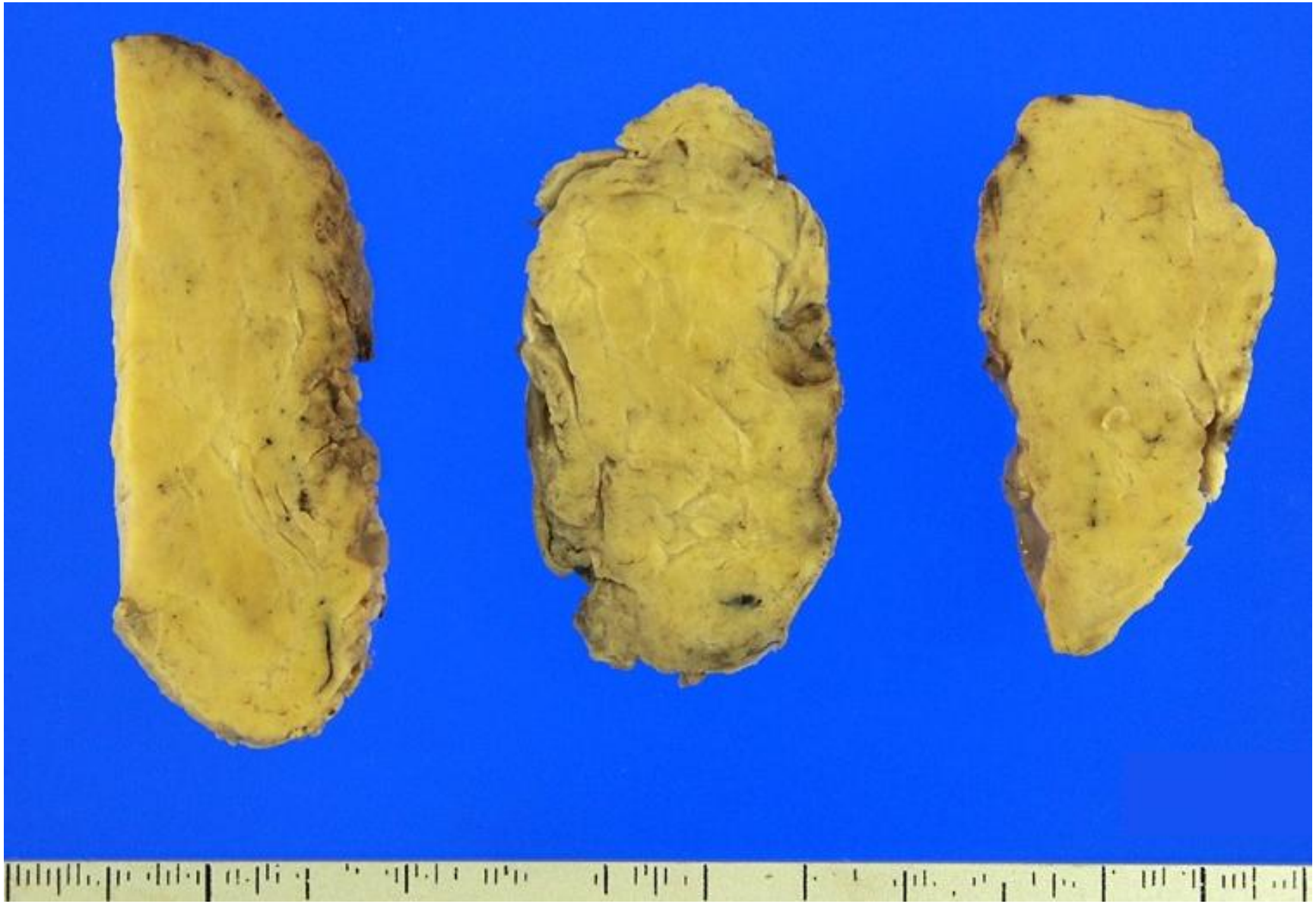
Mitochondria in the epithelial cell of the distal renal tubule.
Cristae are clustered as tubular structures.



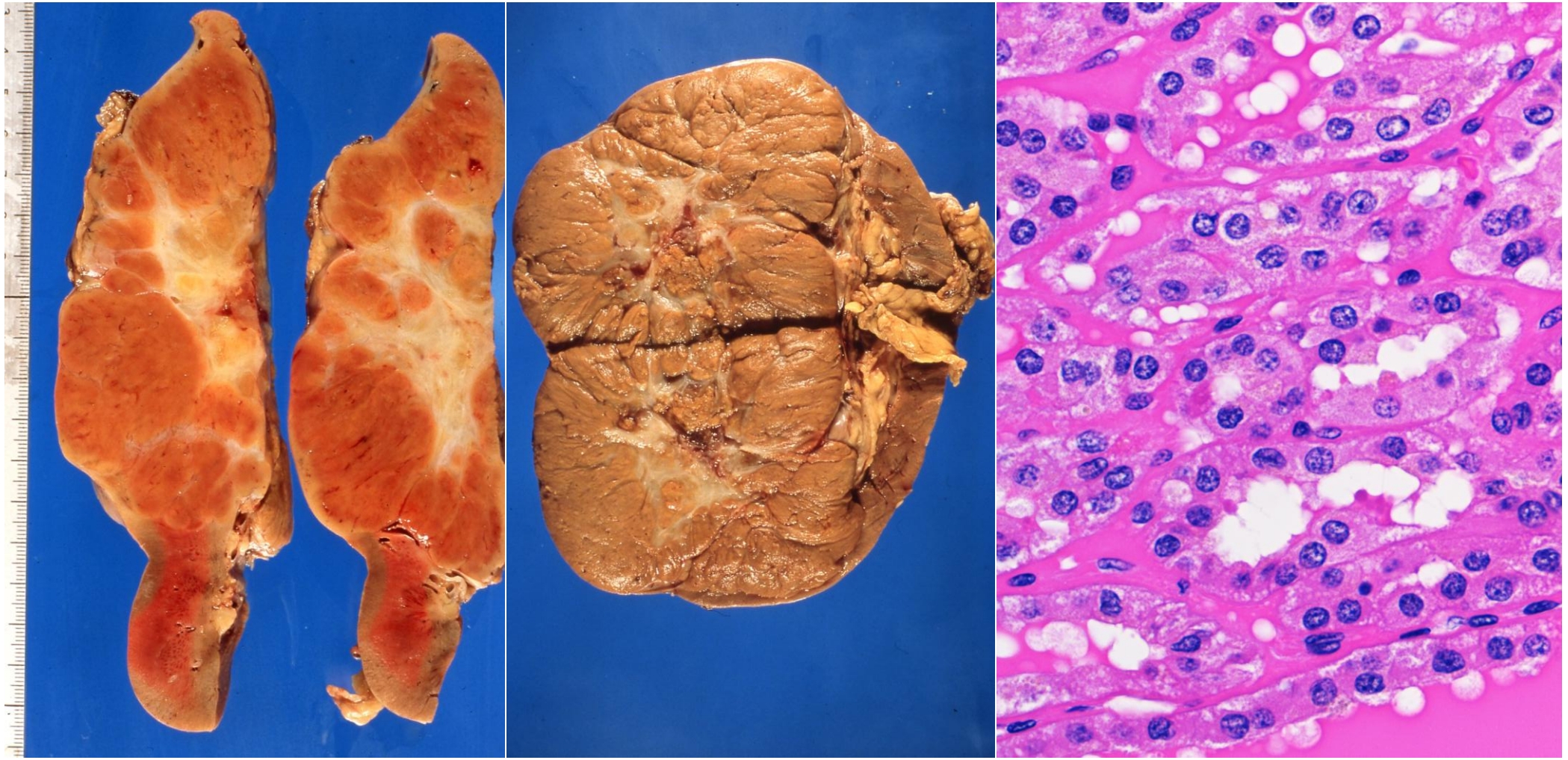
Mitochondria in the steroid-producing adrenocortical cell.
Cristae are vesicular in shape.



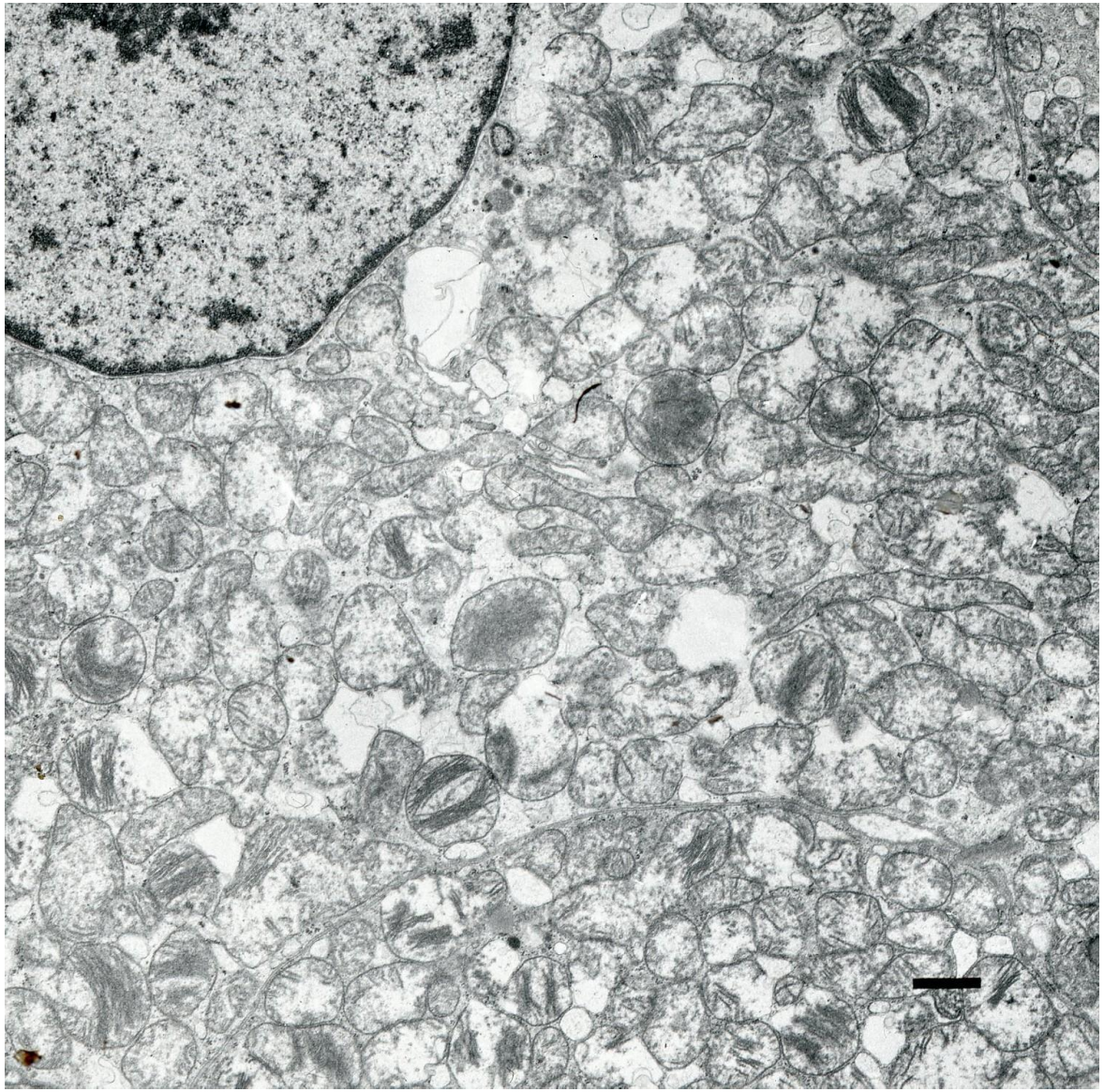
Brown fat cells in the periadrenal region of a normal human adult. Finely vacuolated cytoplasm is characteristic of brown colored fat cells (left: H&E). Ultrastructurally, the brown fat cells are rich in mitochondria among the fat droplets (right). The rich presence of mitochondria gives brownish color for the brown fat cells, thermogenetic cells.



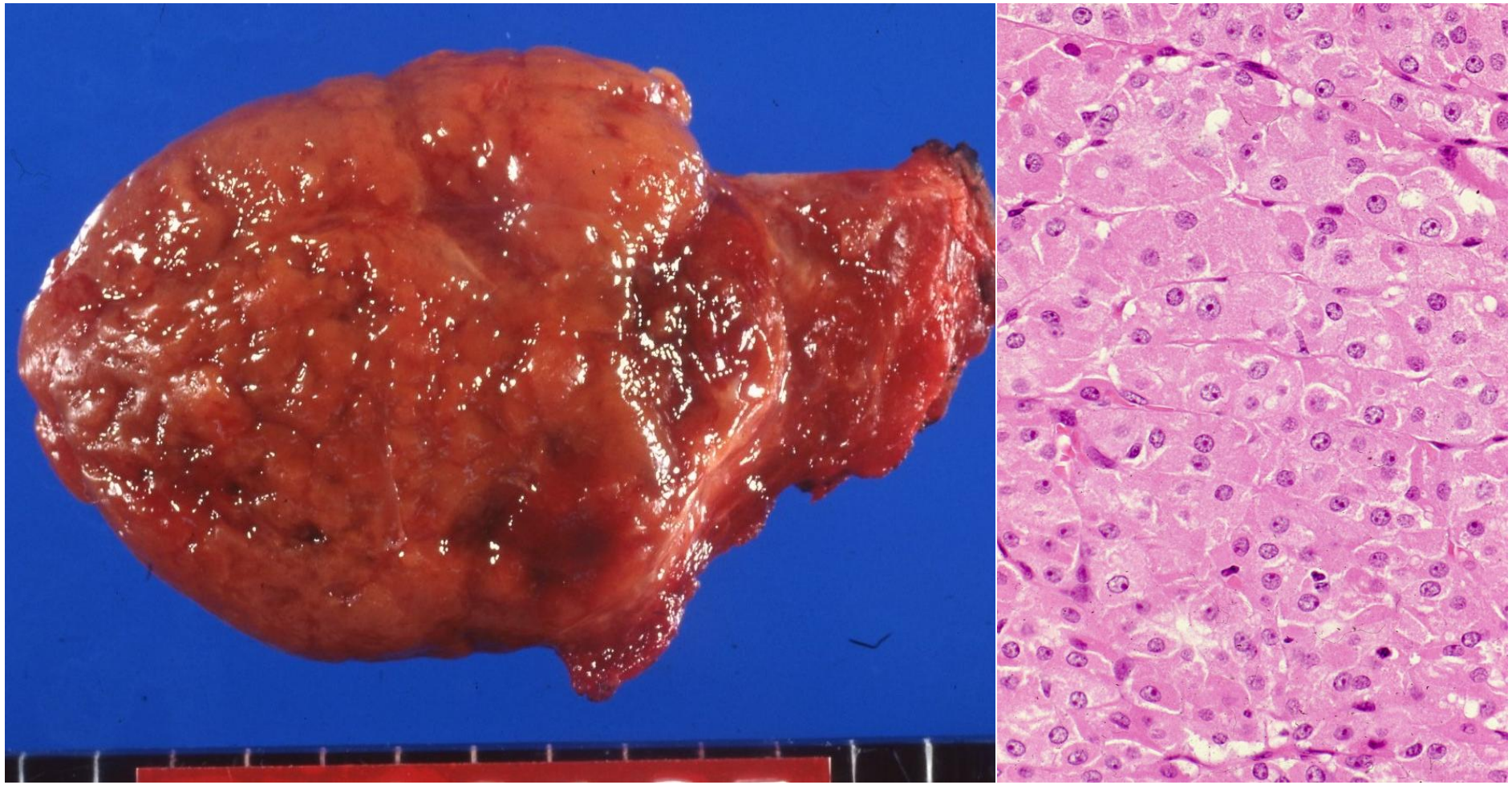
Cut surfaces of hibernoma, a benign tumor of brown fat cells after formalin fixation. Brownish yellow color is characteristic. Brown fat cells are developed in hibernating animals, hence the term hibernoma.



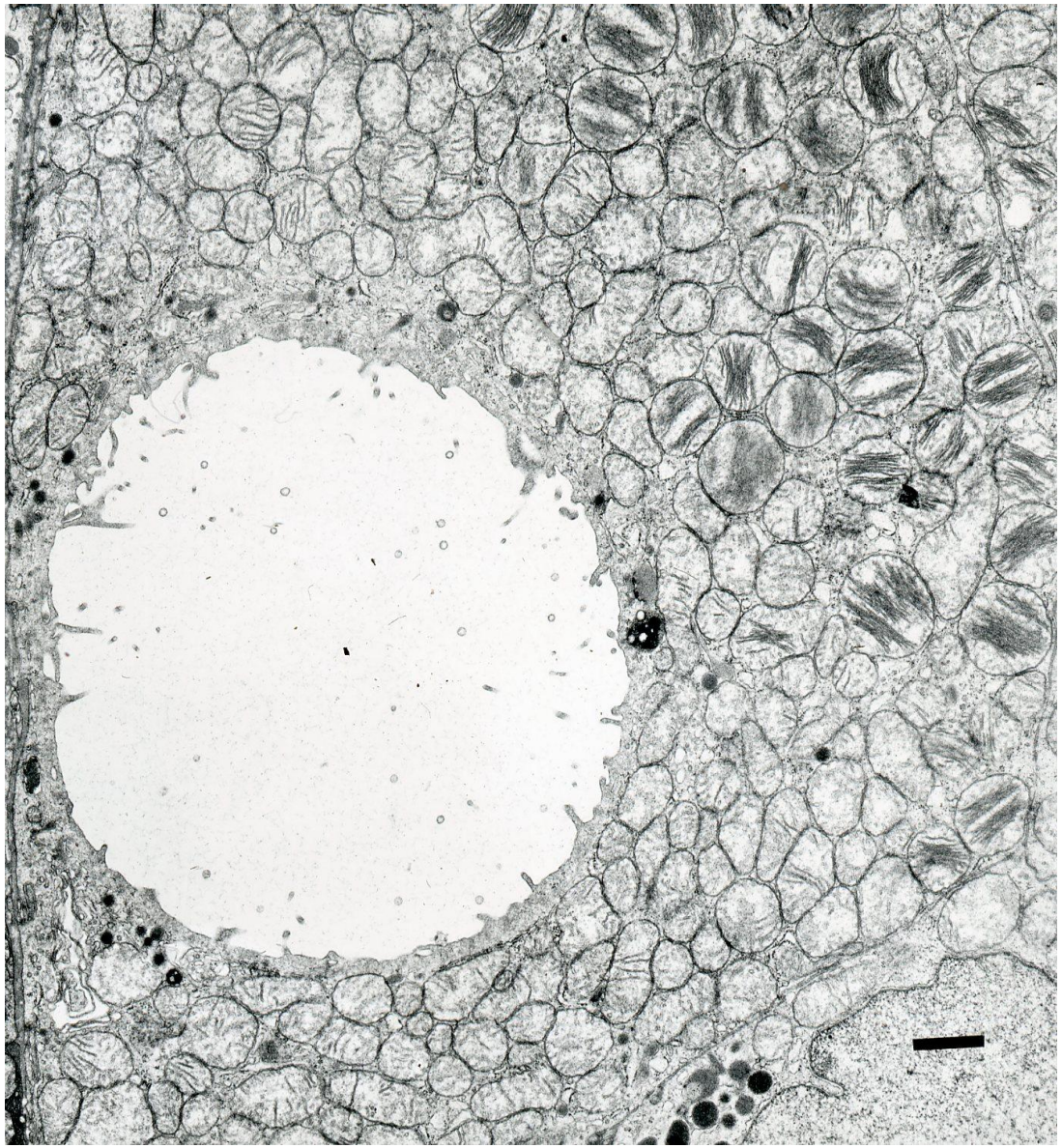
Renal oncocytoma seen in a female patient aged 40's. Cut surfaces of the oncocytoma before (left) and after (center) formalin fixation. Reddish color is noted before fixation, and after fixation brownish color is noted. Microscopically, the tumor cells possess plump eosinophilic and granular cytoplasm due to the rich presence of mitochondria (right: H&E). Oncocytoma is nicknamed as mitochondrioma.



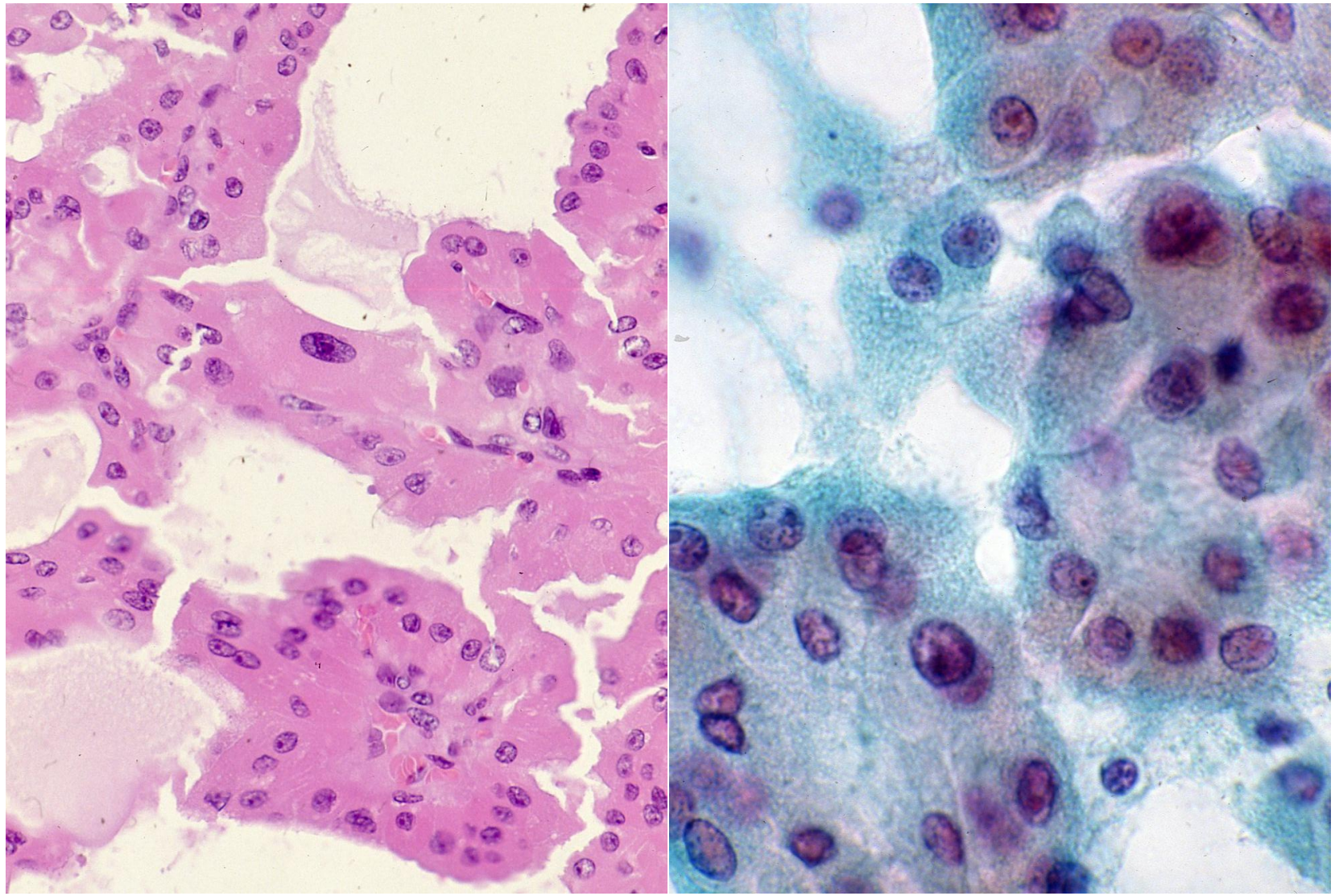
Ultrastructure of renal oncocytoma. The cytoplasm is filled with mitochondria. Oncocytoma is nicknamed as mitochondrioma.



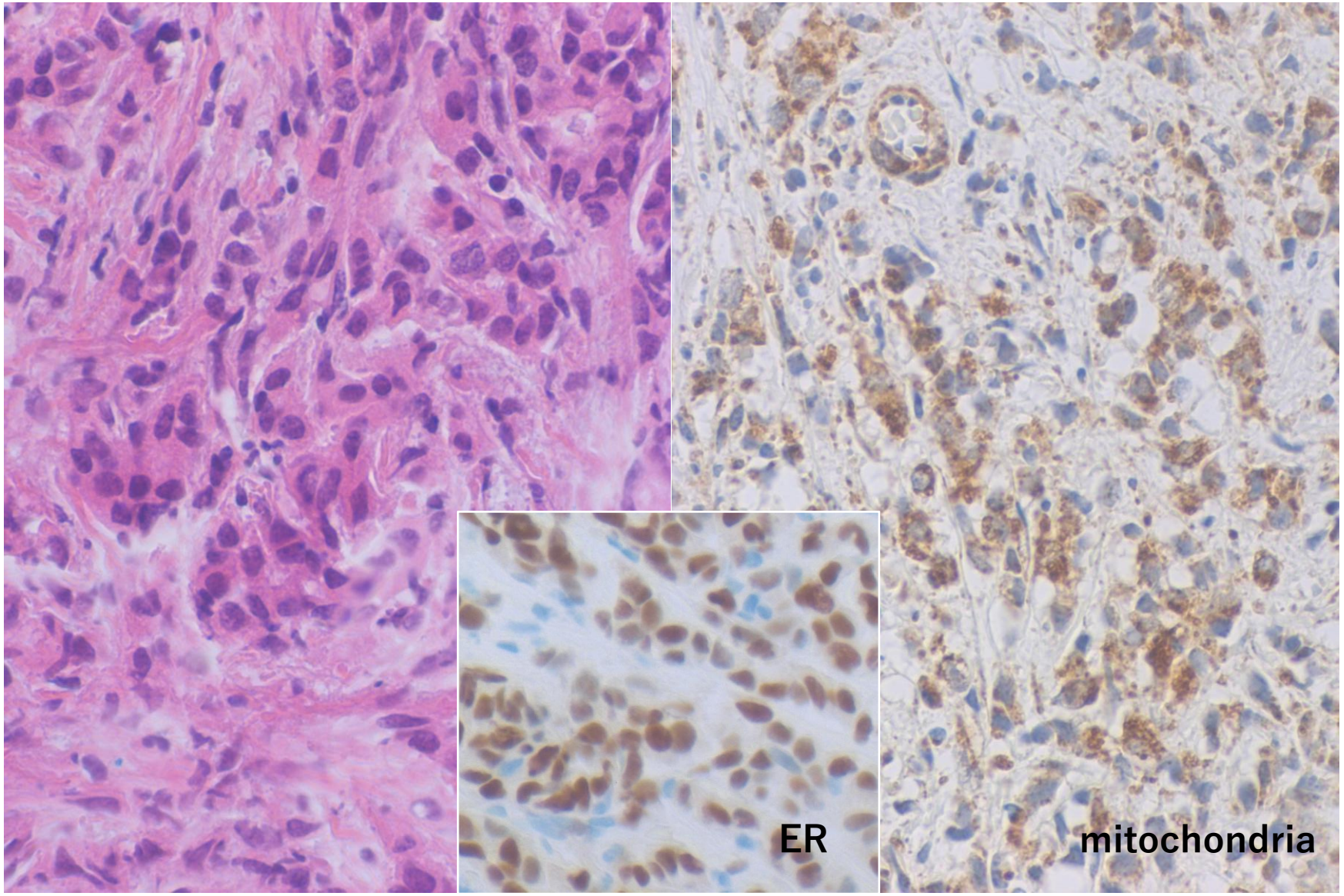
Thyroid oncocytoma in a 63 y-o female patient. Gross appearance (left) is characterized by its brownish color. The bulging of the cut surface of the tumor indicates high cellularity and high intratumoral pressure. Microscopically, monomorphous tumor cells possess plump eosinophilic granular cytoplasm (right: H&E).



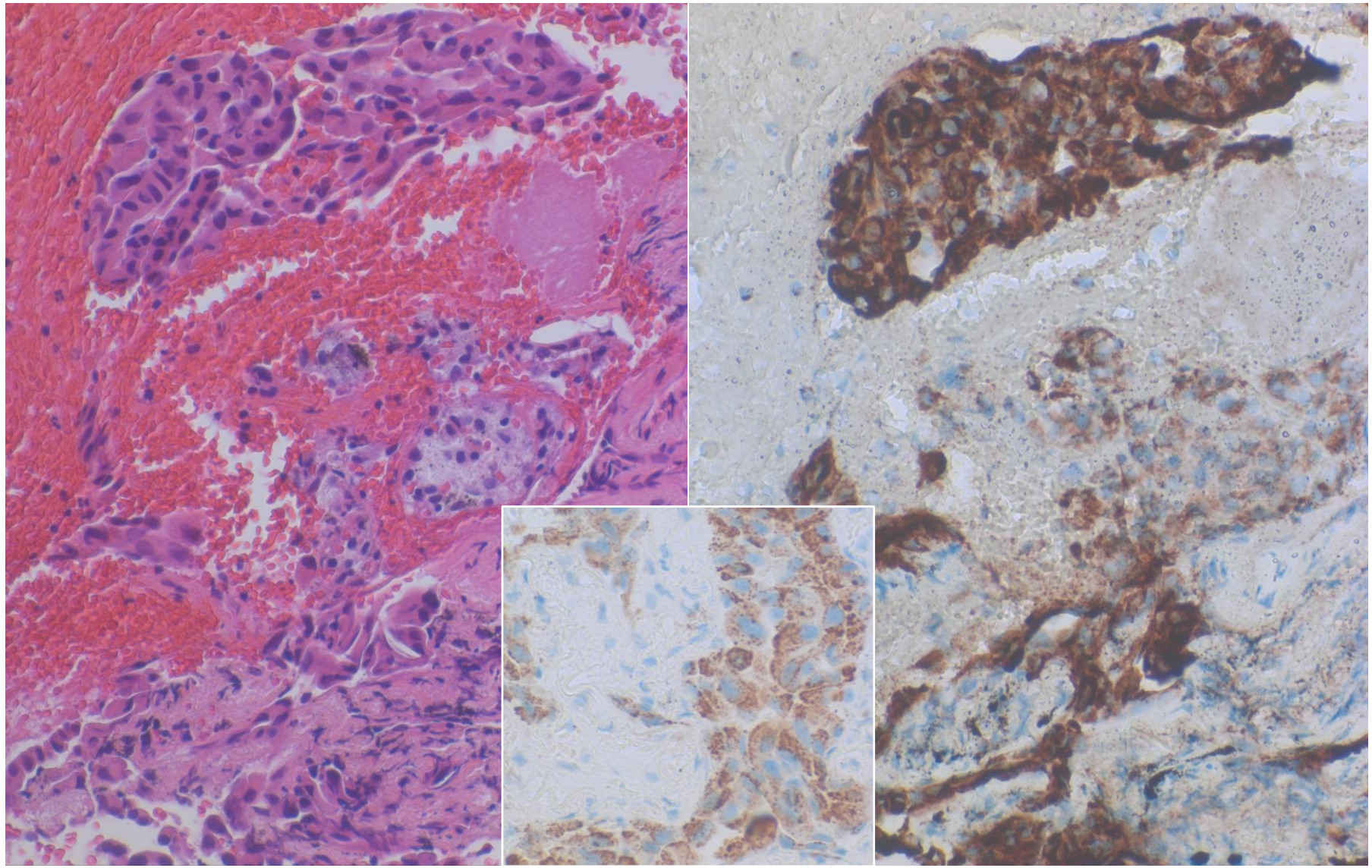
Ultrastructure of thyroid oncocytoma. The cytoplasm is filled with mitochondria. An intracytoplasmic lumen lined by sparse microvilli is observed. Oncocytoma is nicknamed as mitochondrioma.



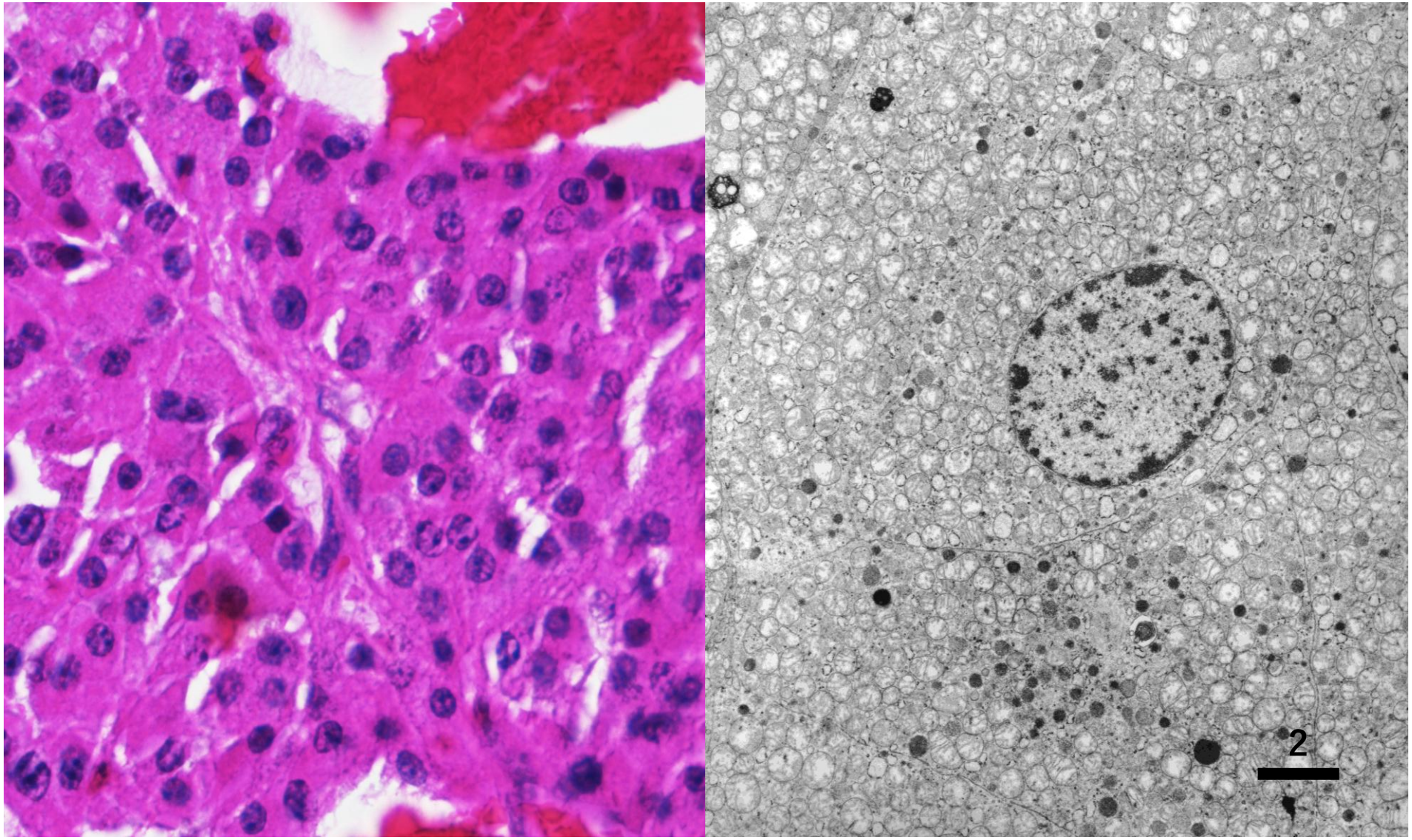
Thyroid oncocytic carcinoma (Hürthle cell carcinoma) in a 50 y-o female patient. Atypical oncocytic cancer cells show a papillary growth pattern (left: H&E). Nuclear pleomorphism is discerned. Aspiration cytology reveals anisonucleosis and distinct plump granular cytoplasm (right: Papanicolaou).



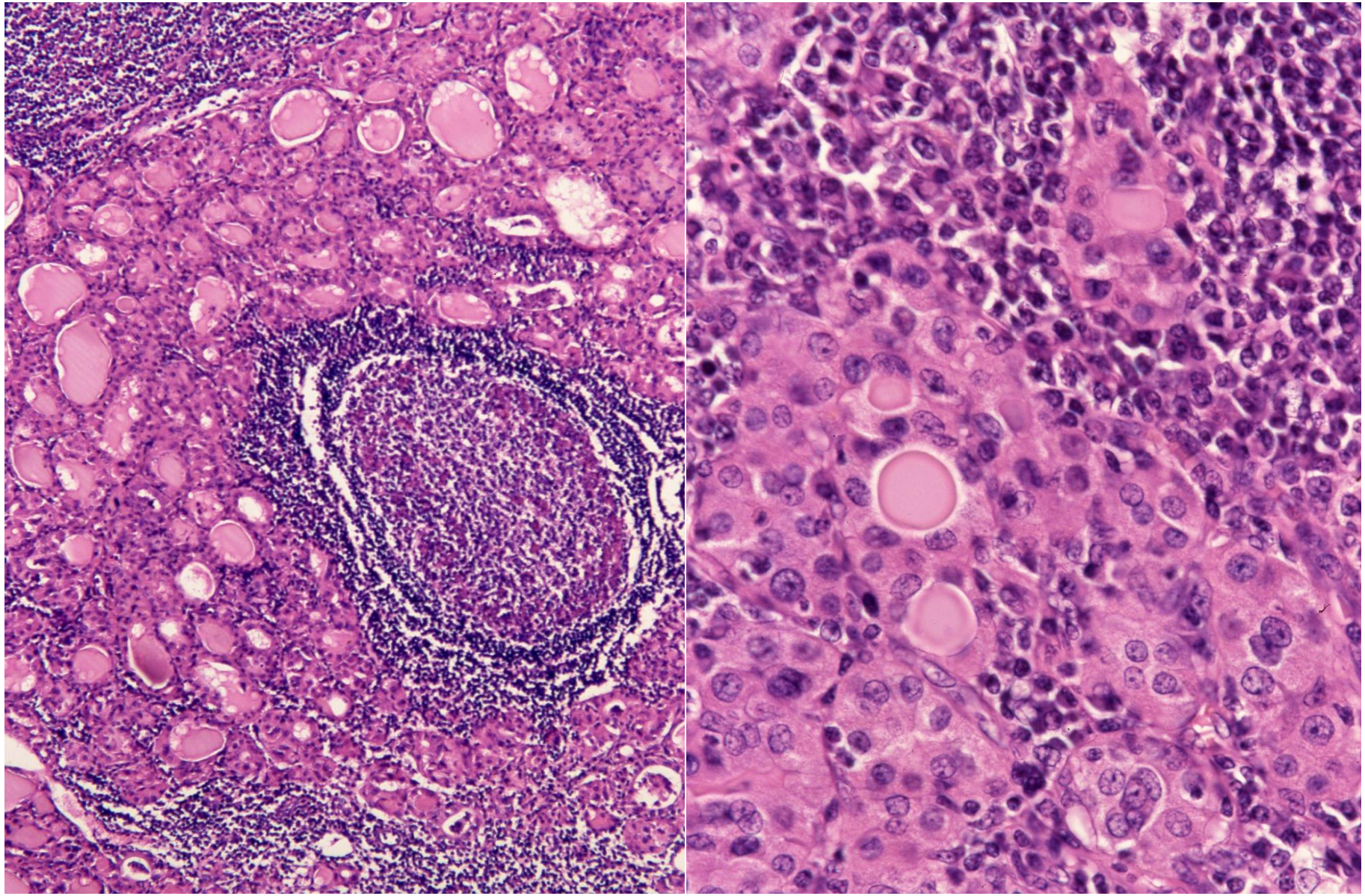
Oncocytic carcinoma of the breast of a 73 y-o female patient. Invasive ductal carcinoma cells possess plump eosinophilic cytoplasm (left: H&E). The cytoplasm is rich in mitochondria (right: immunostaining for mitochondria). The cancer cells diffusely express ER (inset: immunostaining for ER).



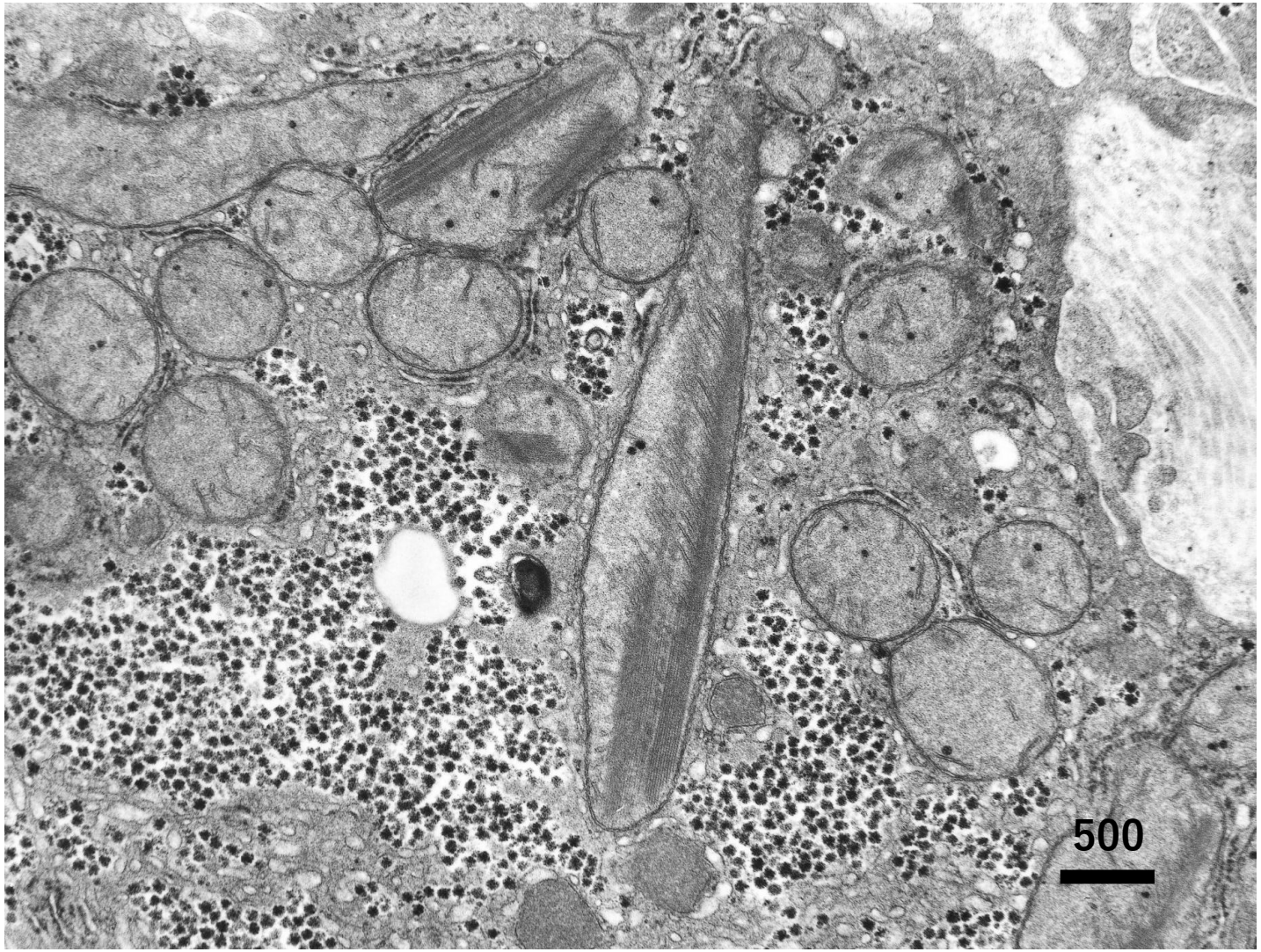
Oncocytic adenocarcinoma of the right upper lobe of the lung of a 75 y-o male patient. TBLB reveals invasive growth of oncocytic cancer cells with plump eosinophilic cytoplasm (left: H&E). The cytoplasm is rich in mitochondria (right: immunostaining for mitochondria). Napsin A immunoreactivity is also demonstrated in the cytoplasm (inset).



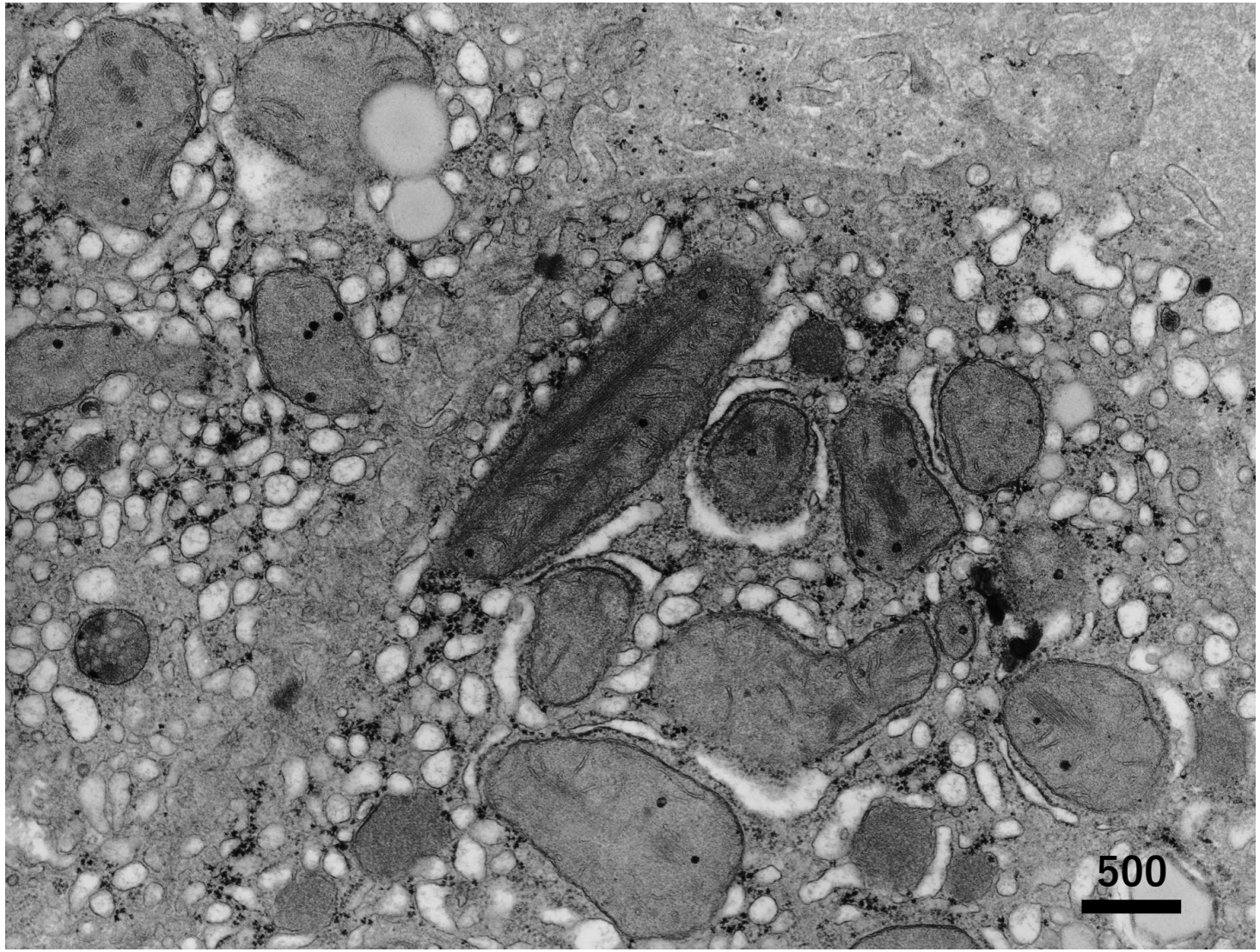
Bronchial carcinoid tumor, oncocytic type, seen in a 78 y-o female patient. The carcinoid tumor cells possess plump eosinophilic cytoplasm. Electron microscopically, the cytoplasm is filled with mitochondria, and neuroendocrine-type cored granules measuring 170-550 nm (mean: 325 nm) are dispersed.



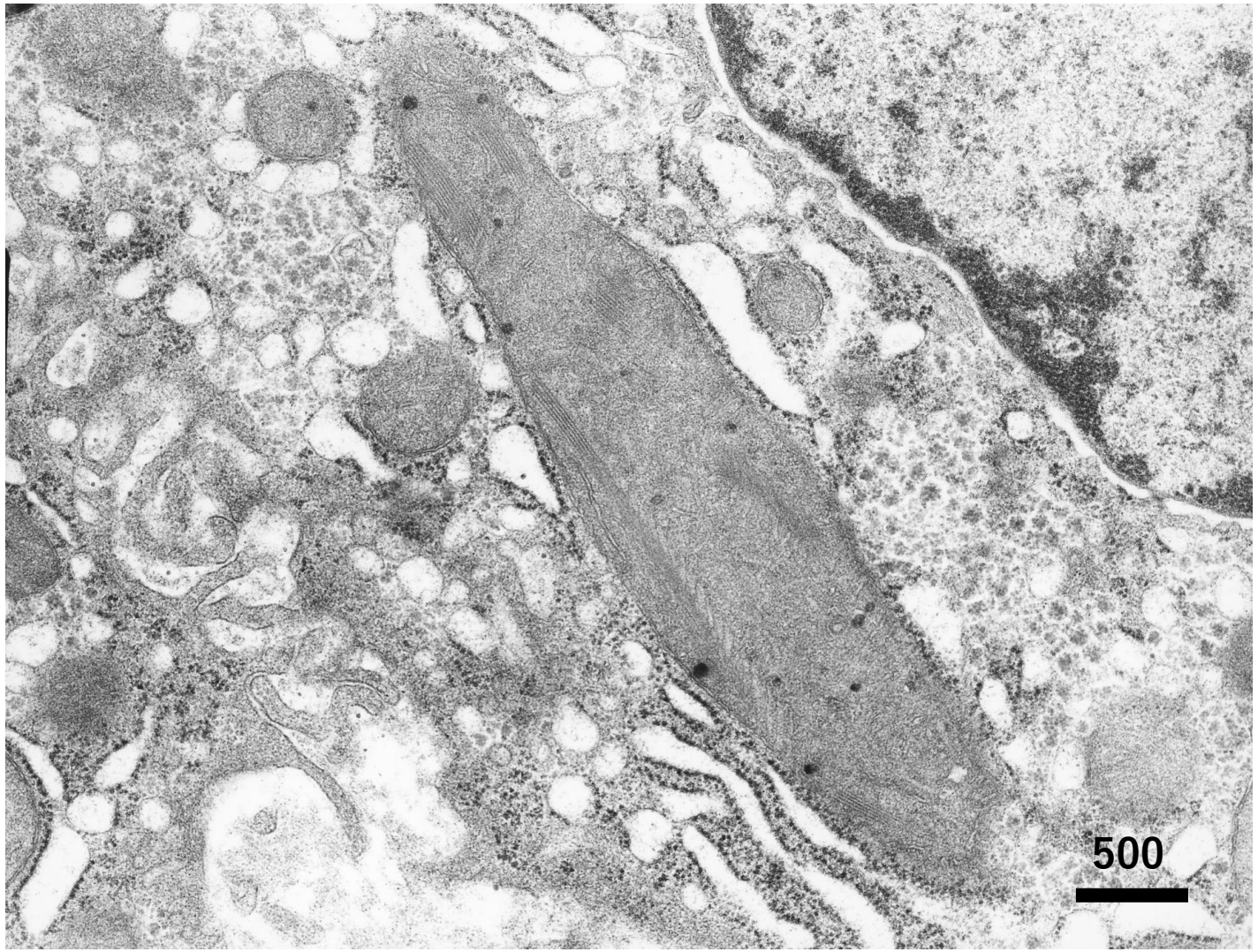
Hashimoto thyroiditis in a 70 y-o female patient. Lymphocytic infiltration with lymphoid follicle formation is evident. The follicular epithelial cells show oncocytic metaplasia, a diagnostic feature of Hashimoto thyroiditis (H&E).



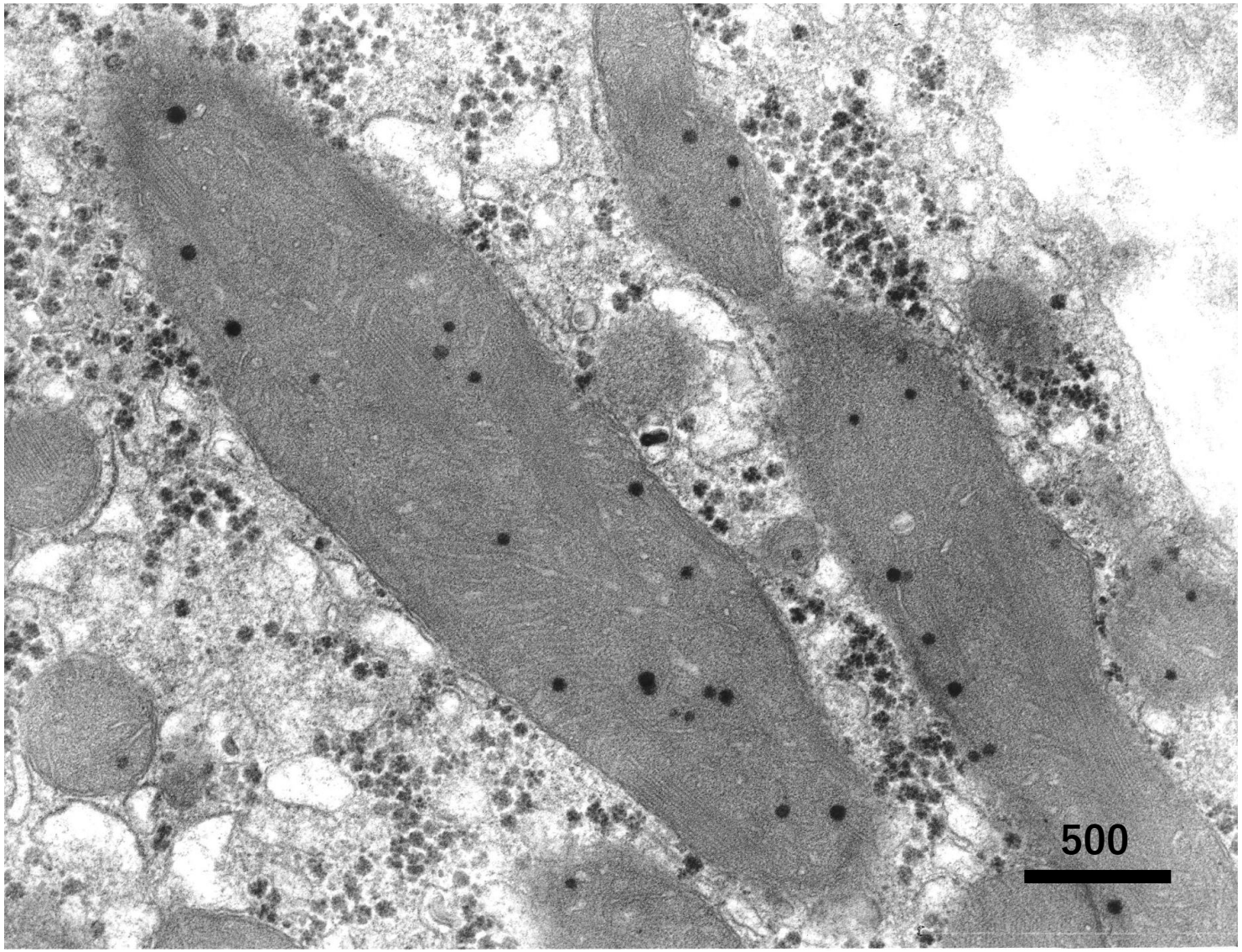
Drug-induced hepatic injury seen in a 49 y-o female patient. She presented with chronic liver dysfunction without hepatitis virus markers. Deposition of longitudinal tubular clusters is seen in the enlarged mitochondrial matrix.



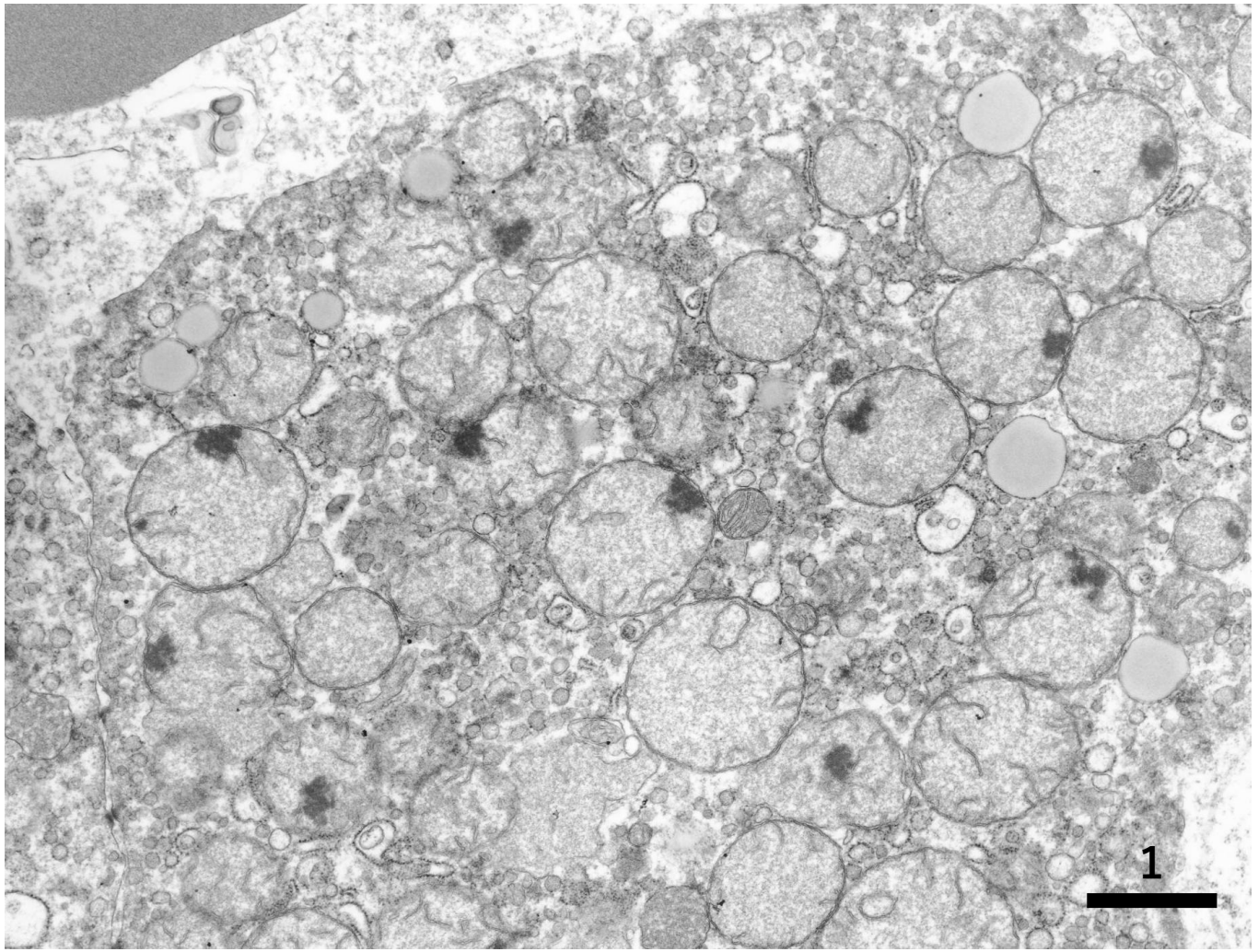
A 4 y-o boy showed mild but chronic hepatic dysfunction. Hepatitis viral markers and autoantibodies are negative. The liver biopsy reveals minimal inflammation. Fine structure of the hepatocyte demonstrates focal mitochondrial abnormality with longitudinal parallel arrangement of the cristae. Increase of peroxisomes is associated.



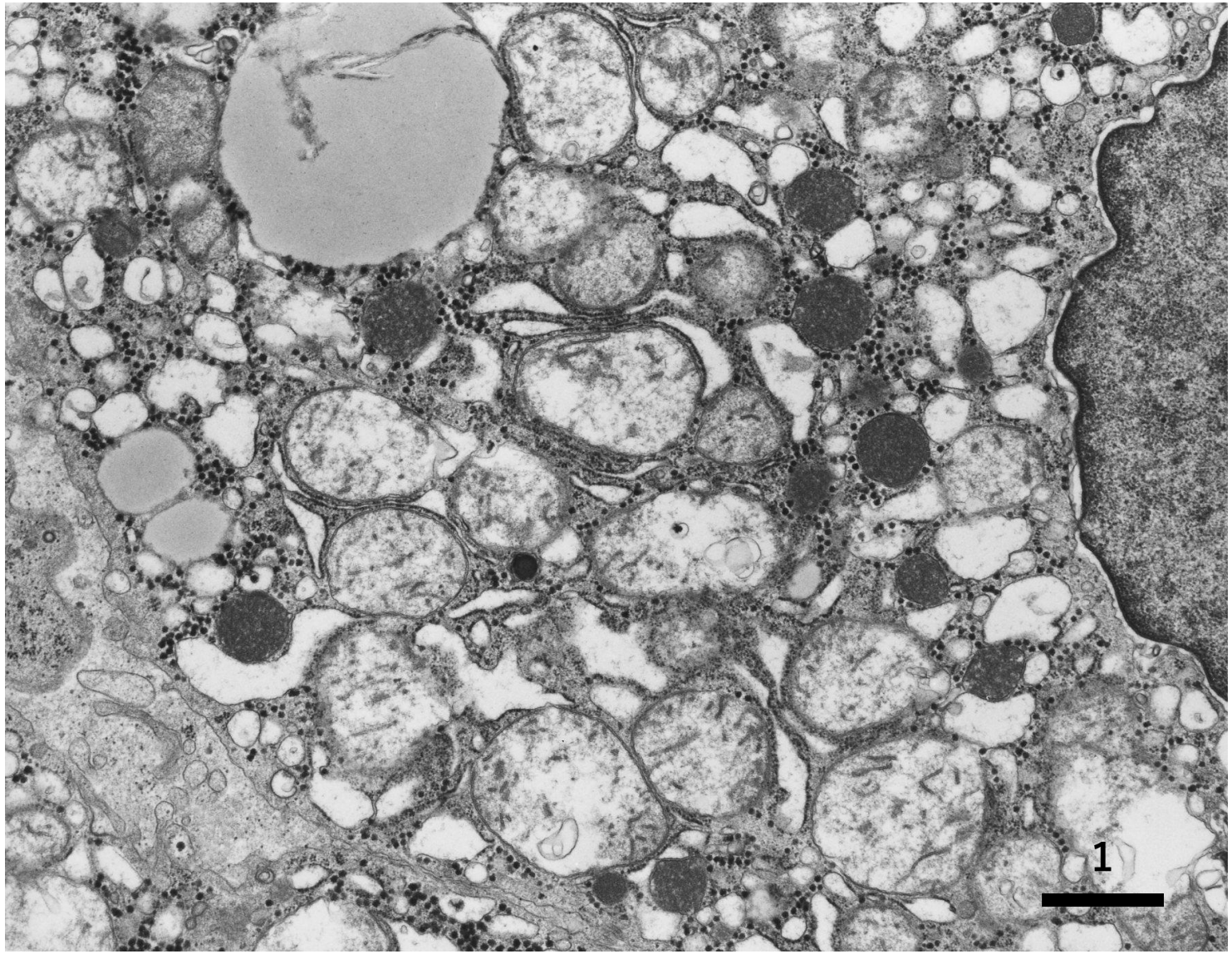
Mild hepatic injury with mild fatty change seen in a 78 y-o female patient. She presented with chronic liver dysfunction without hepatitis virus markers. Deposition of longitudinal lamellar structures is seen in the enlarged mitochondrial matrix. Electron-dense dot-like structures (nucleoids), representing mitochondrial DNA, are also dispersed in the matrix.



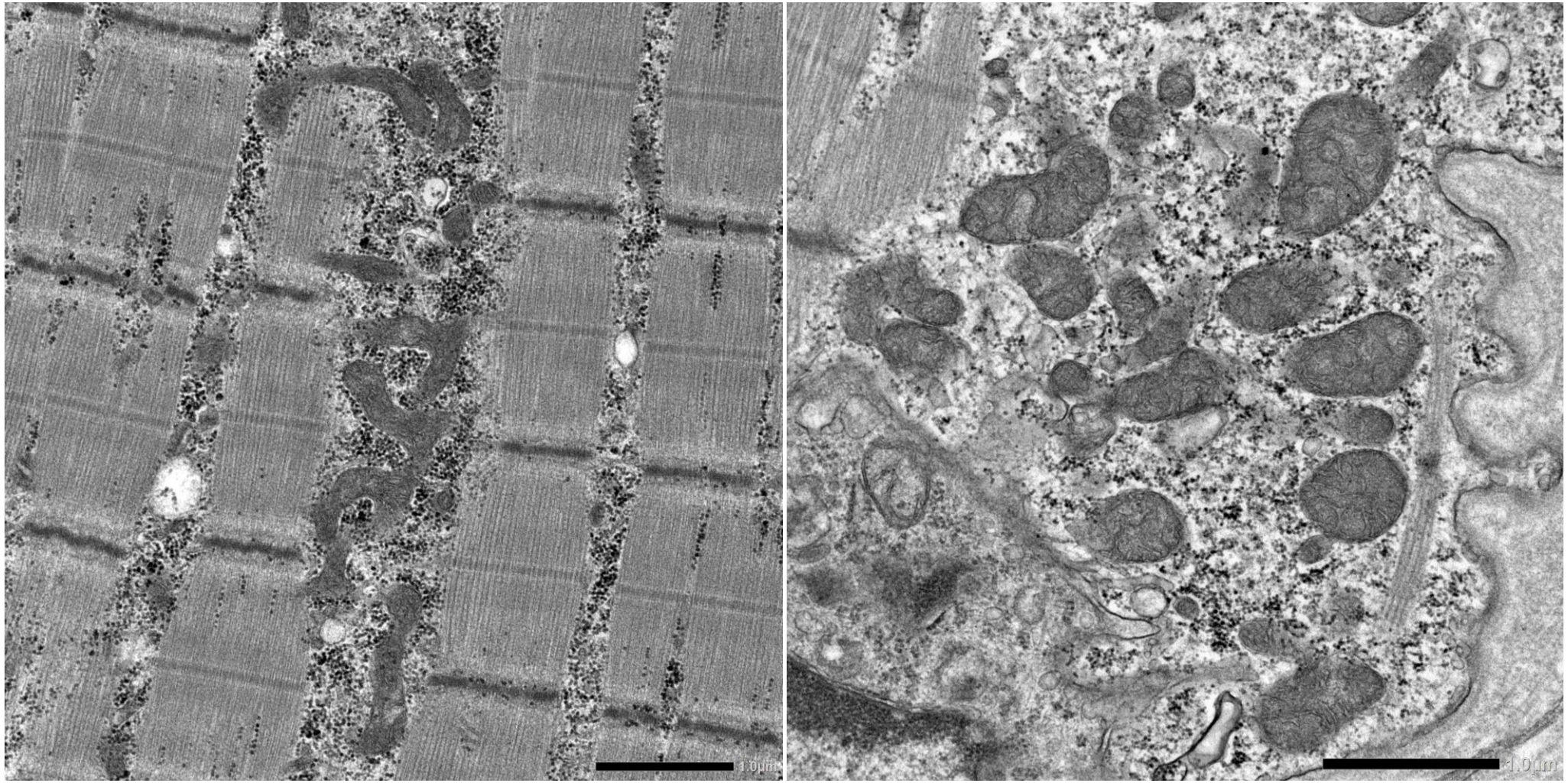
Giant mitochondria in the hepatocyte with liver fibrosis seen in a 46 y-o male patient. He presented with chronic liver dysfunction without hepatitis markers. Tubular longitudinal rearrangement of the cristae is seen in the enlarged mitochondrial matrix. Numbers of electron-dense nucleoids (mitochondrial DNA) are scattered.



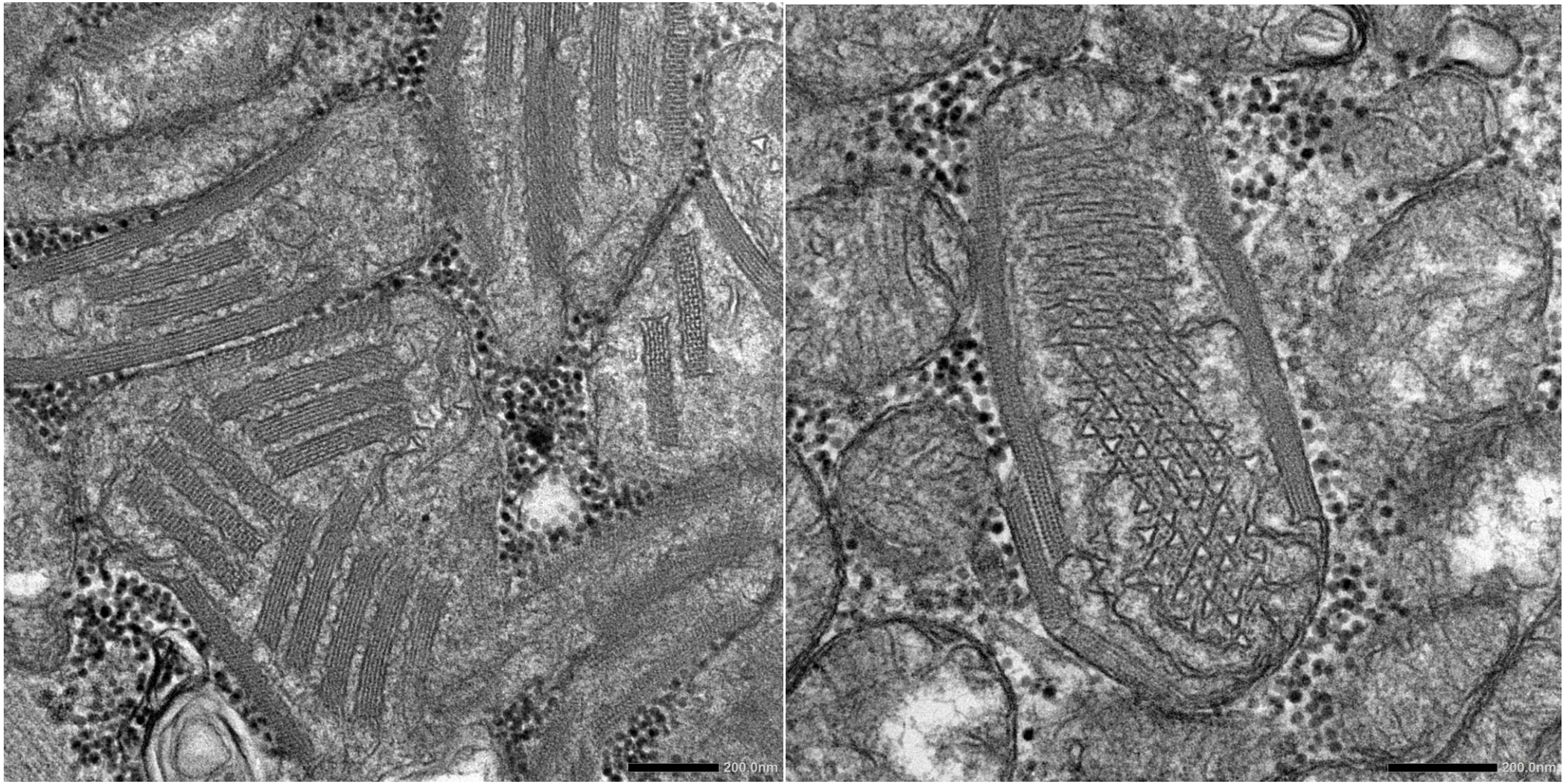
Reye syndrome seen in a 6 months-old boy. After taking antipyretics for high fever caused by influenza virus infection, he died from acute encephalopathy, and necropsy was taken from the liver. Ultrastructurally, cristae are often lost. Large aggregations of the nucleoid (mitochondrial DNA) are seen. Aggregation of the nucleoids occurs when the mitochondrial function is suppressed. Ref. Ban-Ishihara R, et al. Dynamics of nucleoid structure regulated by mitochondrial fission contributes to cristae reformation and release of cytochrome c. Proc Natl Acad Sci USA 2013; 110(29): 11863-11868. doi: 10.1073/pnas.1301951110



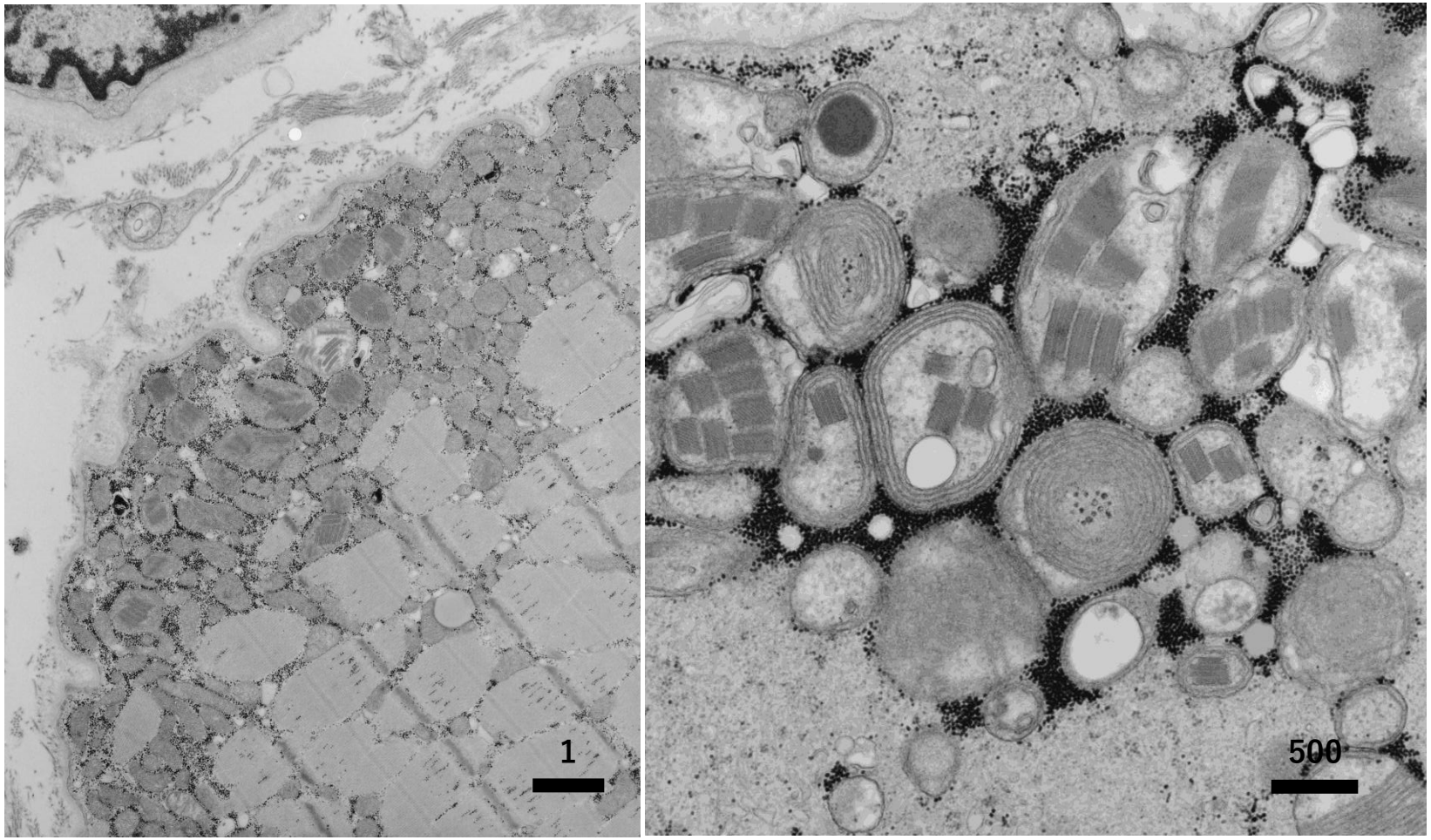
Reye syndrome seen in a 6 months-old girl, manifesting acute encephalopathy and fatty liver of fine droplet type. She took aspirin for high fever caused by acute viral infection. Loss or fragmentation of cristae is ultrastructurally characteristic of this disorder with mitochondrial insufficiency. Fatty change of small droplet type is associated. Peroxisomes are activated.



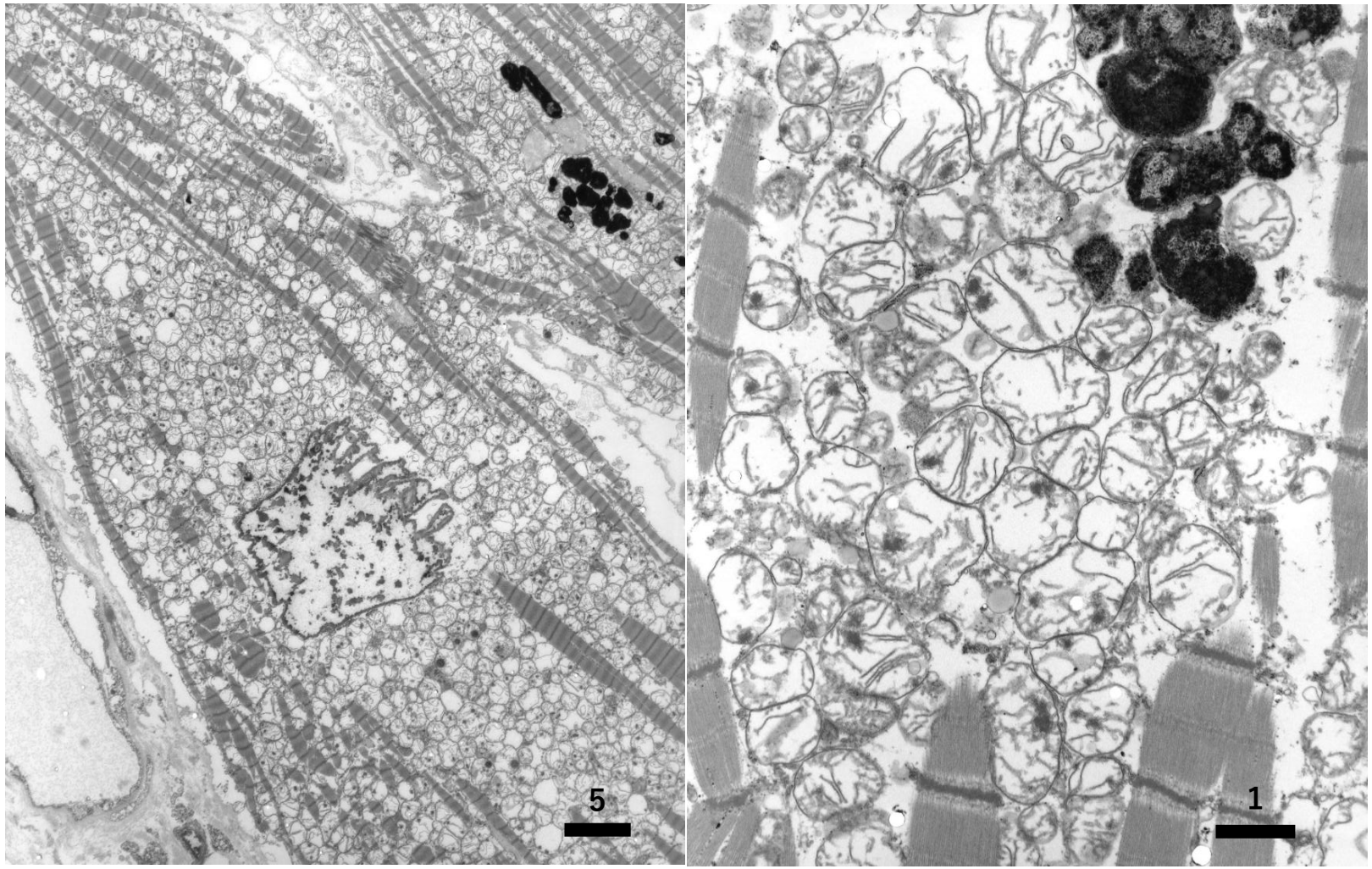
Myositis positive for anti-mitochondria antibodies in a 36 y-o female patient. She complained of muscle weakness of the upper extremities with elevated serum creatine kinase at 600-700 IU/L. Ultrastructurally, no abnormality is seen in the mitochondria.



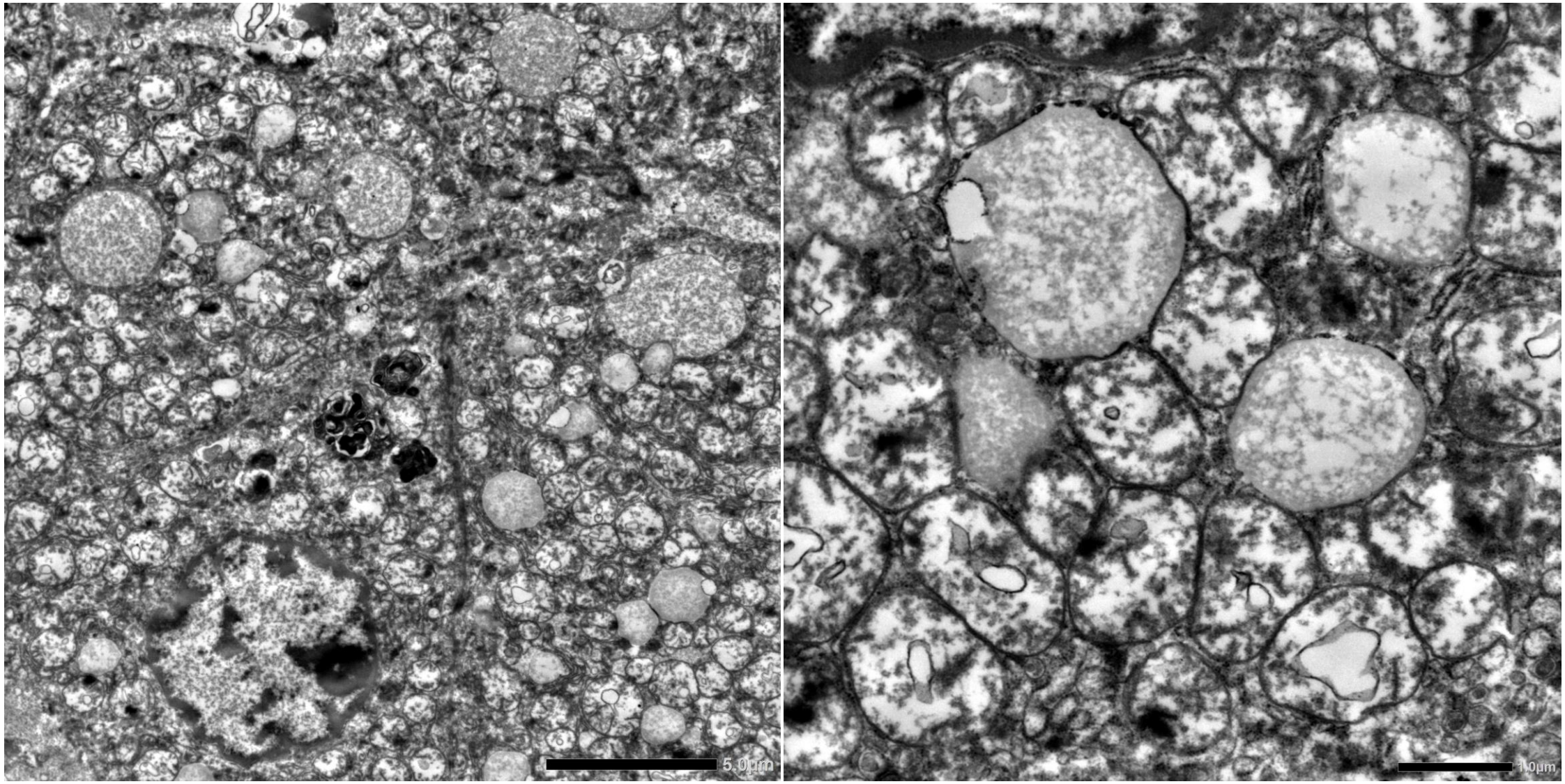
Mitochondriopathy of the striated muscle seen in a 73 y-o female patient. She manifested acute heart failure. Difficulty in hearing and cerebellar atrophy were complicated. Striated muscle biopsy reveals marked increase of mitochondria, particularly along the plasma membrane. Fine morphologic abnormalities include deposition of crystalloids with a tubule or lattice-like arrangement



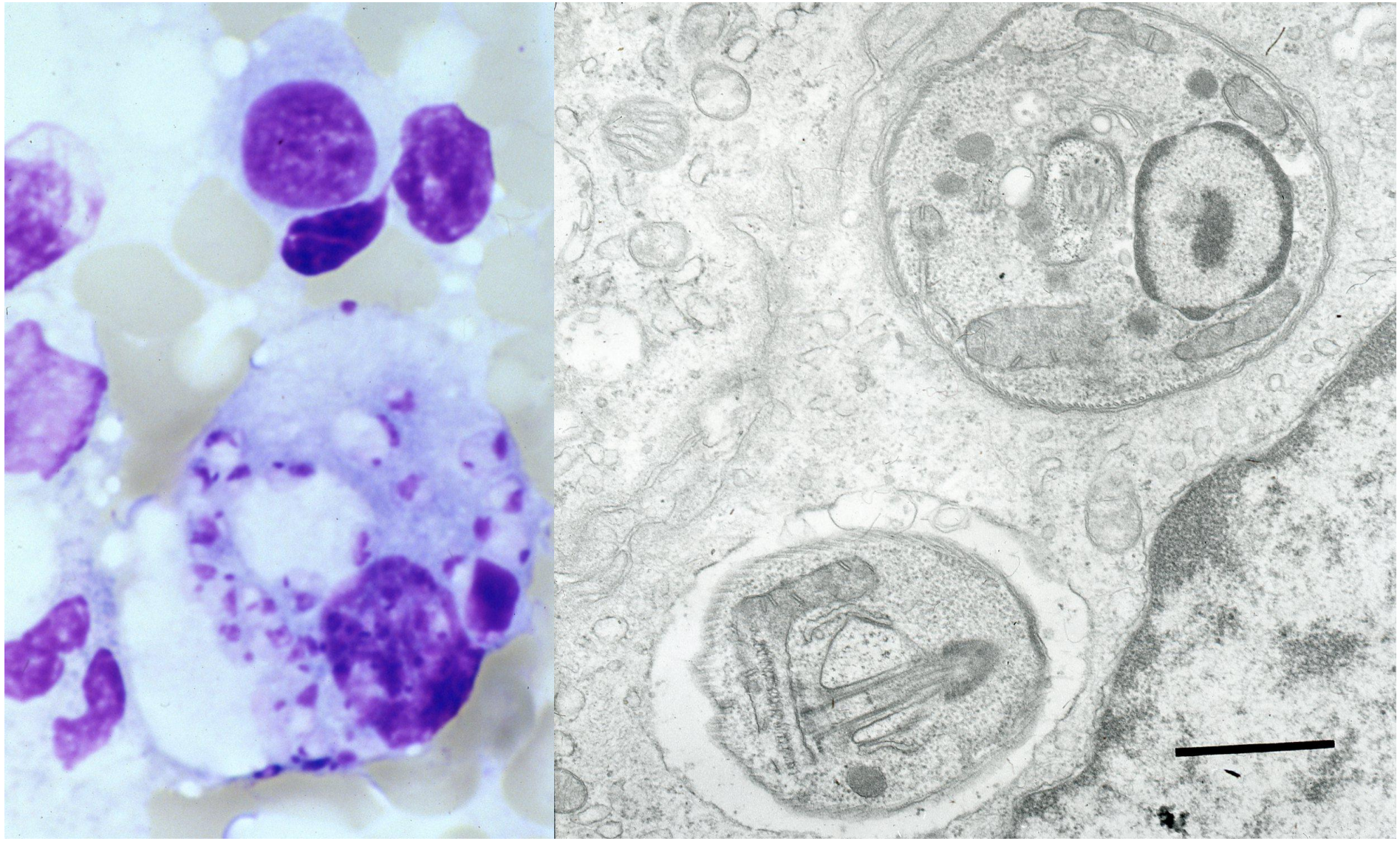
Mitochondrial encephalomyopathy (MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes) in a 36 y-o female patient. Striated muscle biopsy reveals accumulation of abnormally crystallized mitochondria particularly at the periphery of the muscle cells.



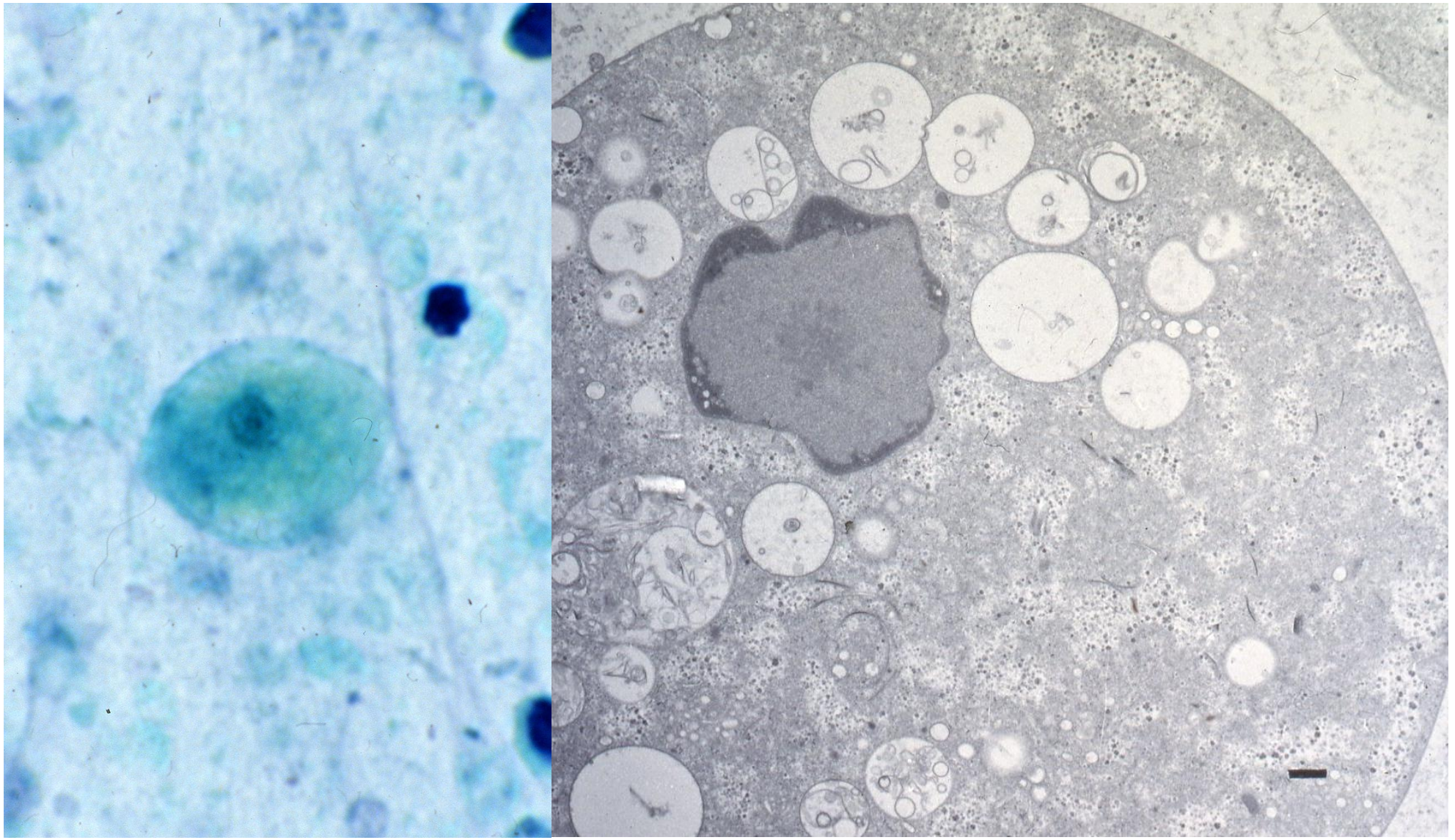
Mitochondriopathy of the heart seen in an autopsy case of 56 y-o male patient. The patient was diagnosed as dilated cardiomyopathy. Marked increase of mitochondria is seen in the cardiomyocyte. Large aggregation of nucleoids, indicating mitochondrial dysfunction, is associated.



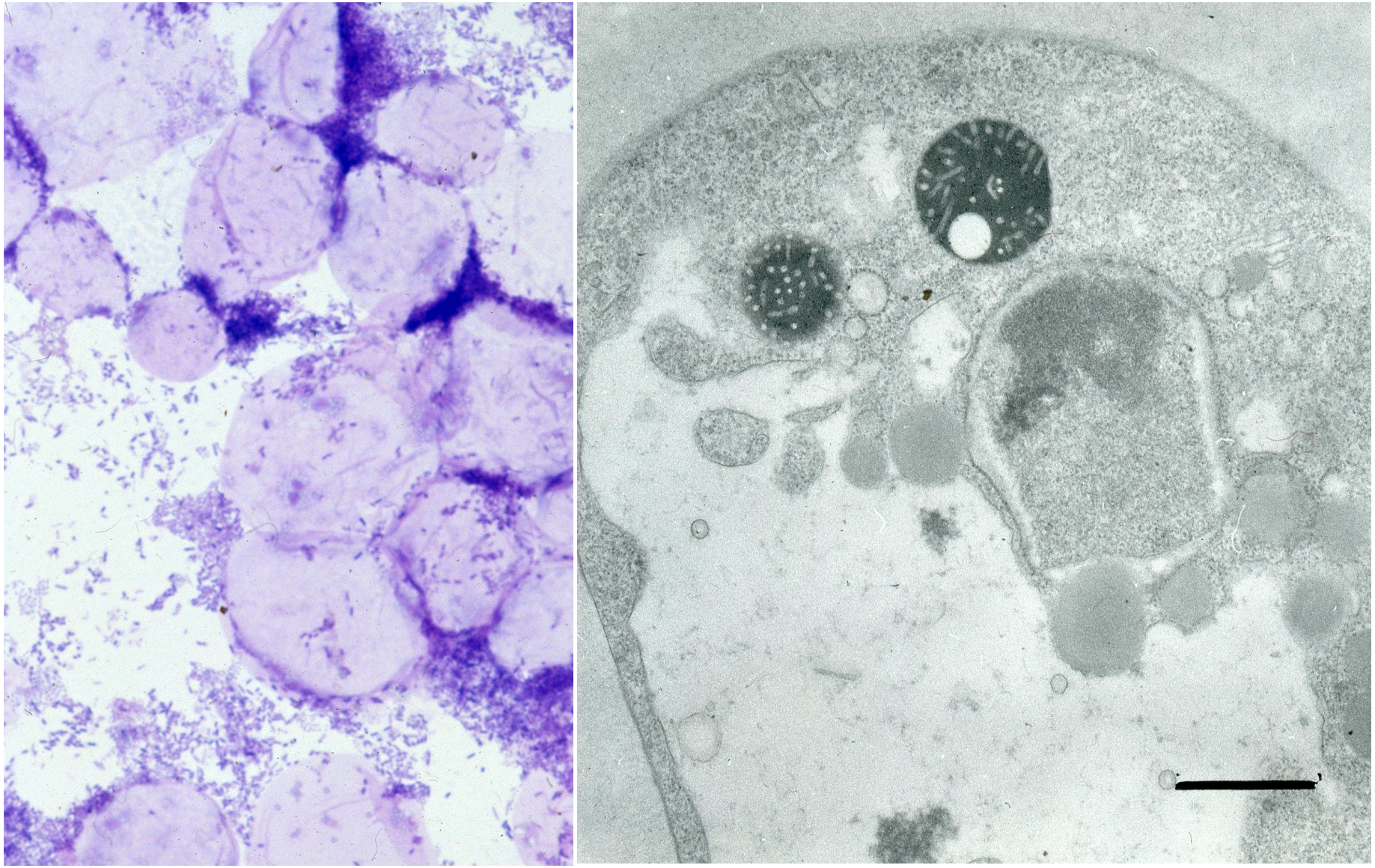
Mitochondriopathy of the liver seen in a 15 y-o girl. Marked increase of mitochondria with their size variation is characteristic. Vesicular change of the cristae and deposition of membranous material in the mitochondrial matrix are discerned .



Cutaneous leishmaniasis of Indian type. Touch smear of the skin biopsy reveals leishmanian bodies in the cytoplasm of a macrophage (left: May-Giemsa). Ultrastructurally, the protozoan cells of *Leishmania tropica* amastigote infected in the macrophage contain mitochondria (right). A kinetoplast (the basal structure of the flagella) is seen, and microtubule are localized along the plasma membrane.



Trophozoite of *Entamoeba histolytica*, an obligate anaerobic protozoa. A Pap-stained trophozoite seen in amebic liver abscess is shown in the left panel. Ultrastructurally, *E. histolytica* contains numbers of vacuoles in the cytoplasm, but lacks mitochondria (right). Among the protozoa, *Giardia lamblia* and *Trichomonas vaginalis* also lack mitochondria.



Blastocystis hominis, an obligate anaerobic a single-celled parasite infecting the human gut. *B. hominis* co-cultured with *E. coli* reveals large cystic structures (left: May-Giemsa). Ultrastructurally, mitochondria with high electron density of the matrix are observed in the *Blastocystis homionis* cell (right). The role of mitochondria in this obligate anaerobic cell is unclear.