EM study for diagnosing neuroferritinopathy

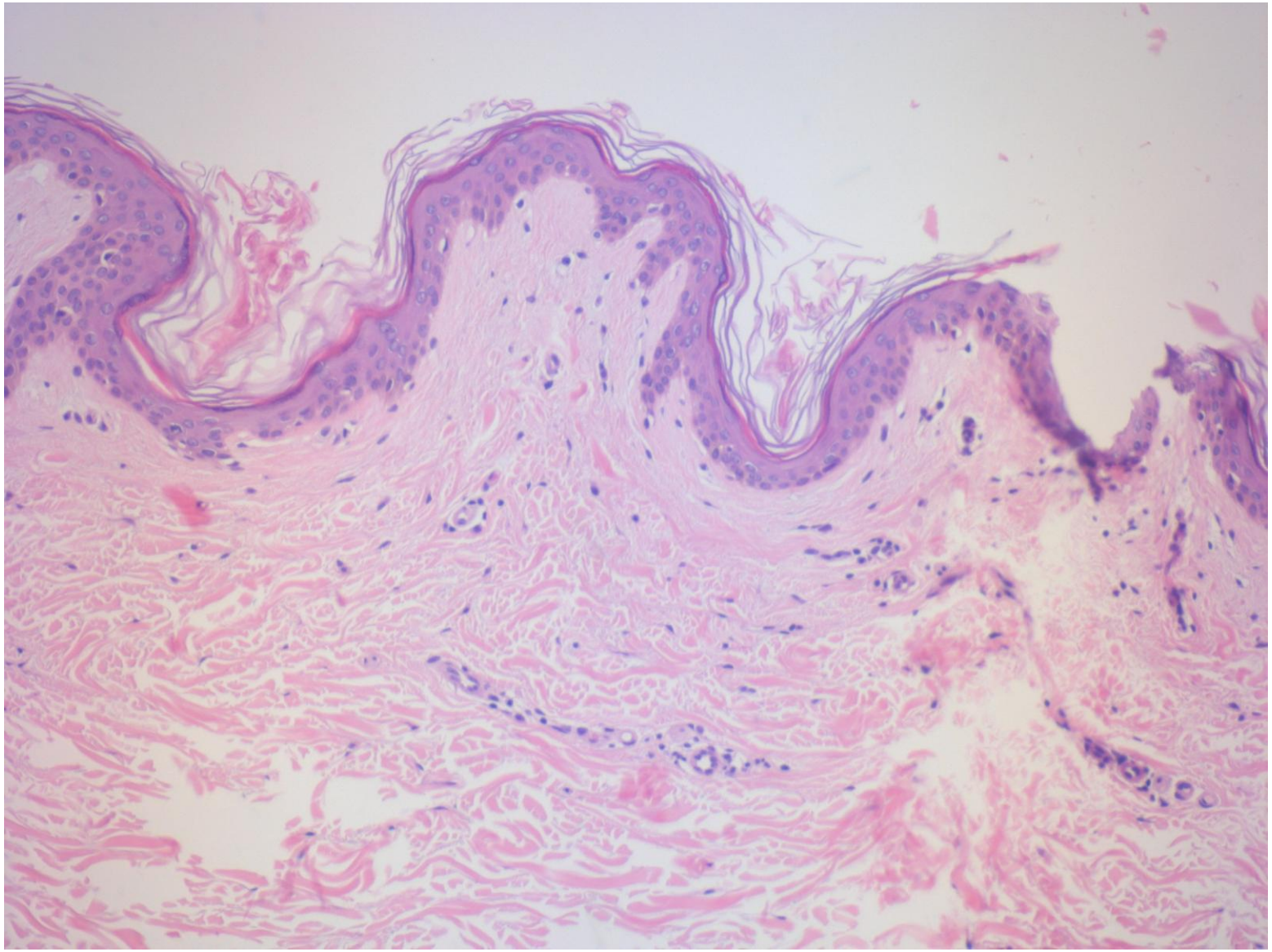
Neuroferritinopathy is an autosomal dominant genetic neurodegenerative disorder characterized by the accumulation of iron in the basal ganglia, cerebellum, and motor cortex of the human brain. Extrapyramidal symptoms such as chorea, dystonia (spasticity, and rigidity) and cognitive deficits progress slowly and generally do not become apparent until adulthood. The disease is caused by mutations in the gene encoding the light chain subunit of the ferritin protein, resulting in decreased iron-binding ability. The mutations provoke accumulation of iron in the brain visualized with MRI. Excessive iron levels catalyze the formation of free radicals via the Fenton reaction, and cause oxidative brain damage. Microscopically, abnormal iron accumulation is seen in the neurons, as well as oligodendroglial and microglial cells, of the striatum and cerebellar cortex, as granular nuclear inclusions. The nuclear inclusions are iron stain-positive and immunoreactive with ferritin antibodies. Serum ferritin levels are normal or low. Reportedly, biopsy from the striated muscle or peripheral nerve is useful for making a diagnosis of this disorder, since similar inclusion bodies are seen.

Skin biopsy was performed in a 59 y-o female case of neuroferritinopathy with a family history. The patient manifested dysarthria and mental disturbance 7 years earlier and cerebellar dysfunction 5 year earlier. Neuroferritinopathy was strongly suspected clinically. Ultrastructural study of the skin biopsy specimen, however, failed to identify intranuclear granular inclusions. Instead, intracytoplasmic vacuoles with fine amorphous vacuolar content are seen in the endothelial cells, smooth muscle cells and fat cells. The etiological significance of these ultrastructural changes whether or not the vacuoles are related to abnormal accumulation of ferritin molecules remains unclear at present.

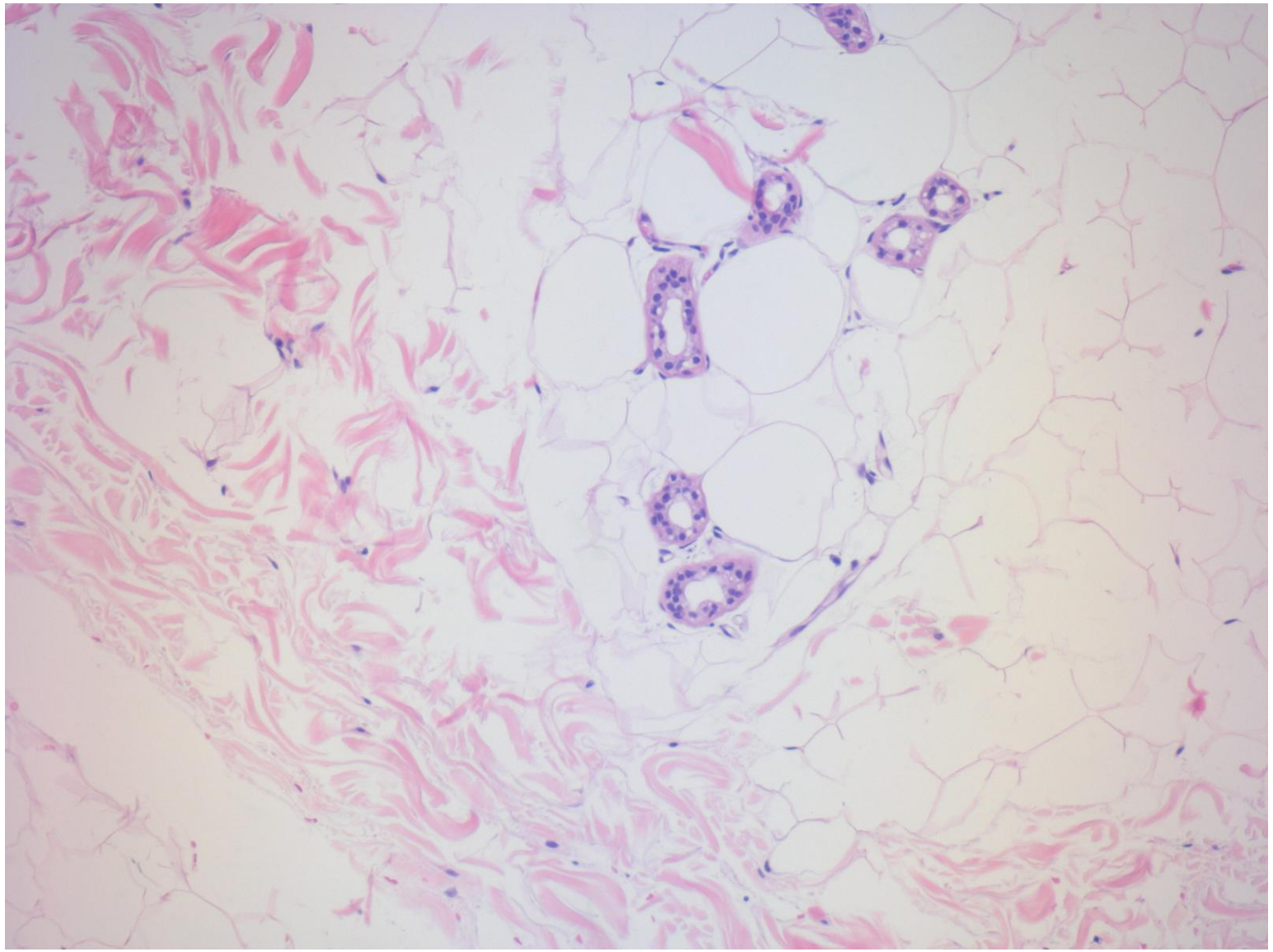
It is of note that mutations of the gene encoding the light chain of ferritin also cause another autosomal dominant hereditary disorder, hyperferritinemia cataract syndrome. Hyperferritinemia cataract syndrome is clinically featured by early onset of cataracts associated with persistently elevated levels of ferritin in the blood plasma. Cataracts are the only known complication associated with this hereditary disorder.

Ref.-1: Schröder, J.M. Ferritinopathy: diagnosis by muscle or nerve biopsy, with a note on other nuclear inclusion body diseases. Acta Neuropathol 2005; 109: 109–114. doi: 10.1007/s00401-004-0949-5

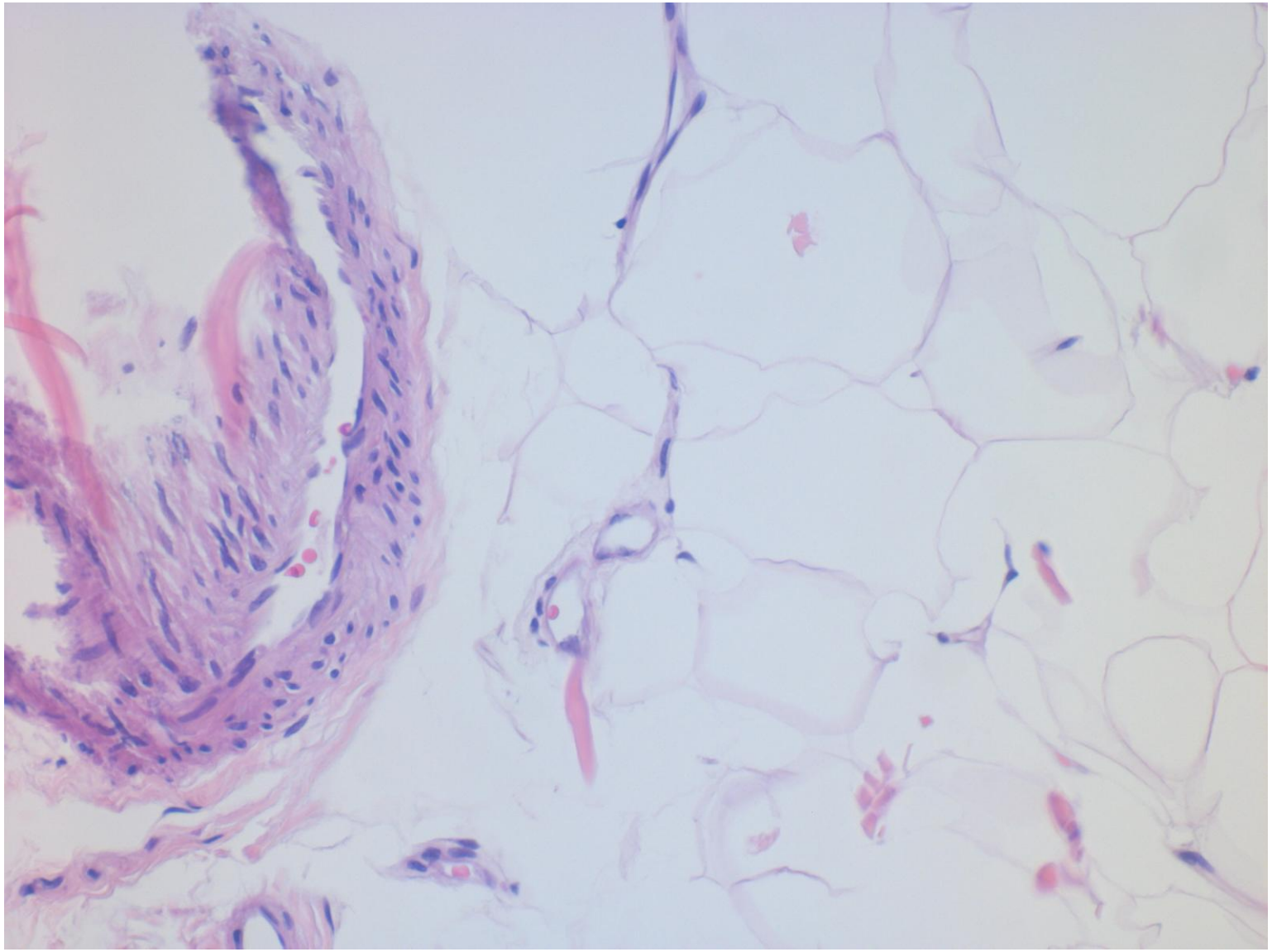
Ref.-2: Celma Nos F, et al. Hereditary hyperferritinemia cataract syndrome: ferritin L gene and physiopathology behind the disease. Report of new cases. Int J Mol Sci 2021; 22(11): 5451. doi: 10.3390/ijms22115451



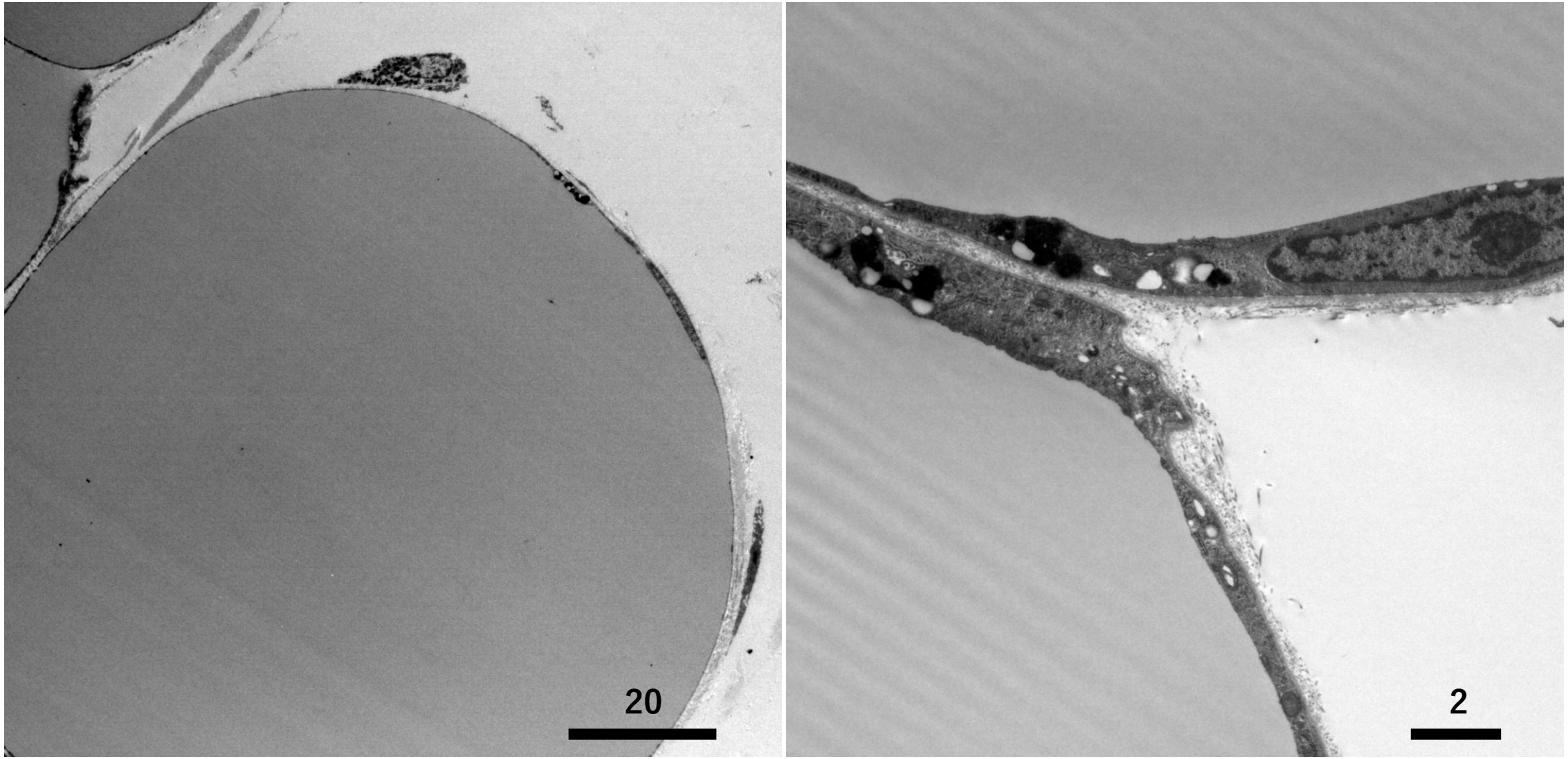
Skin biopsy taken from a 59 y-o female patient clinically suspected of neuroferritinopathy with a family history. No abnormality is discerned in the dermis and epidermis at the light microscopic level (H&E-1).



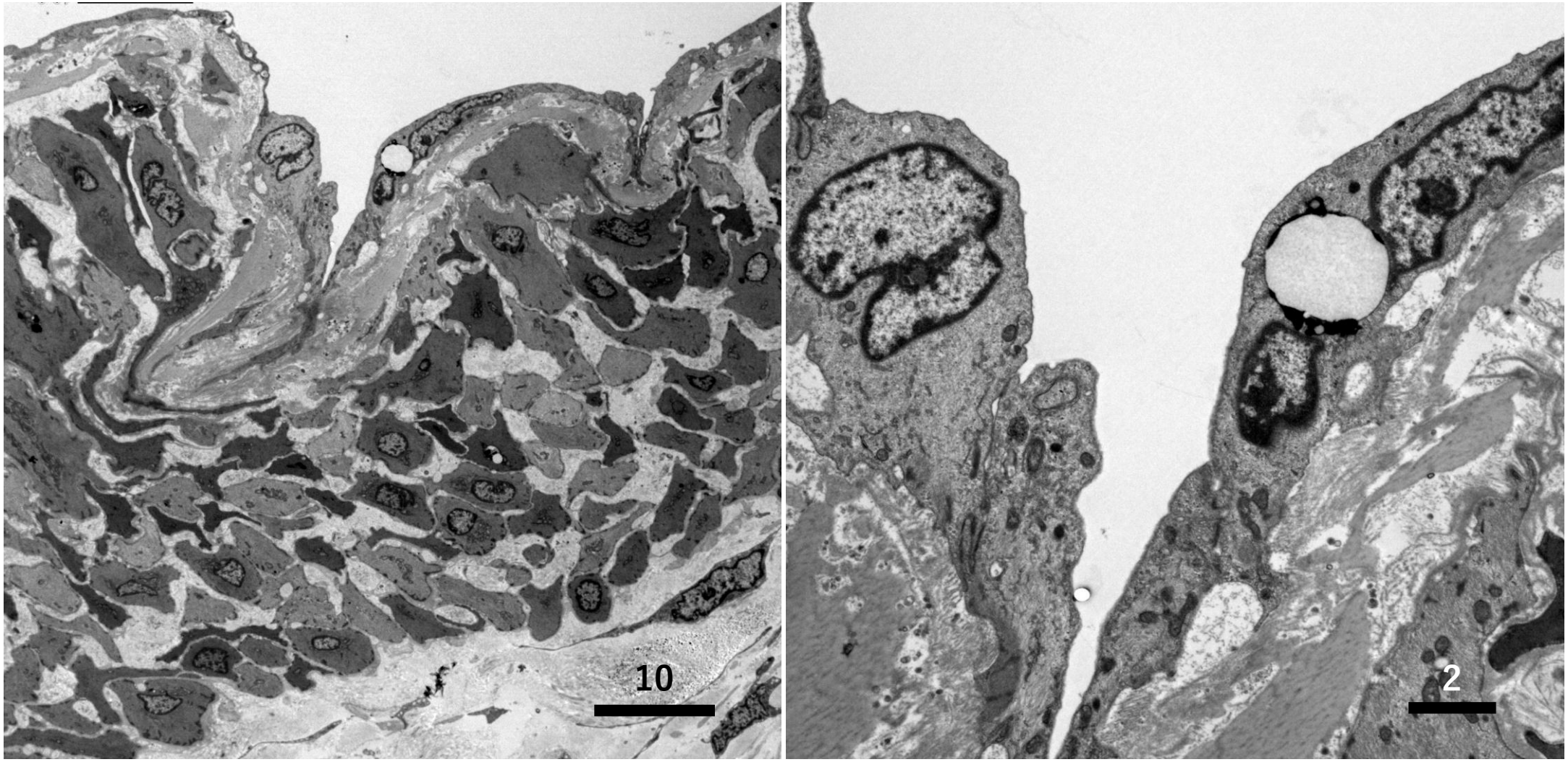
Skin biopsy taken from a 59 y-o female patient clinically suspected of neuroferritinopathy with a family history. No abnormality is discerned in the eccrine sweat gland and subcutaneous fat cells at the light microscopic level (H&E-2).



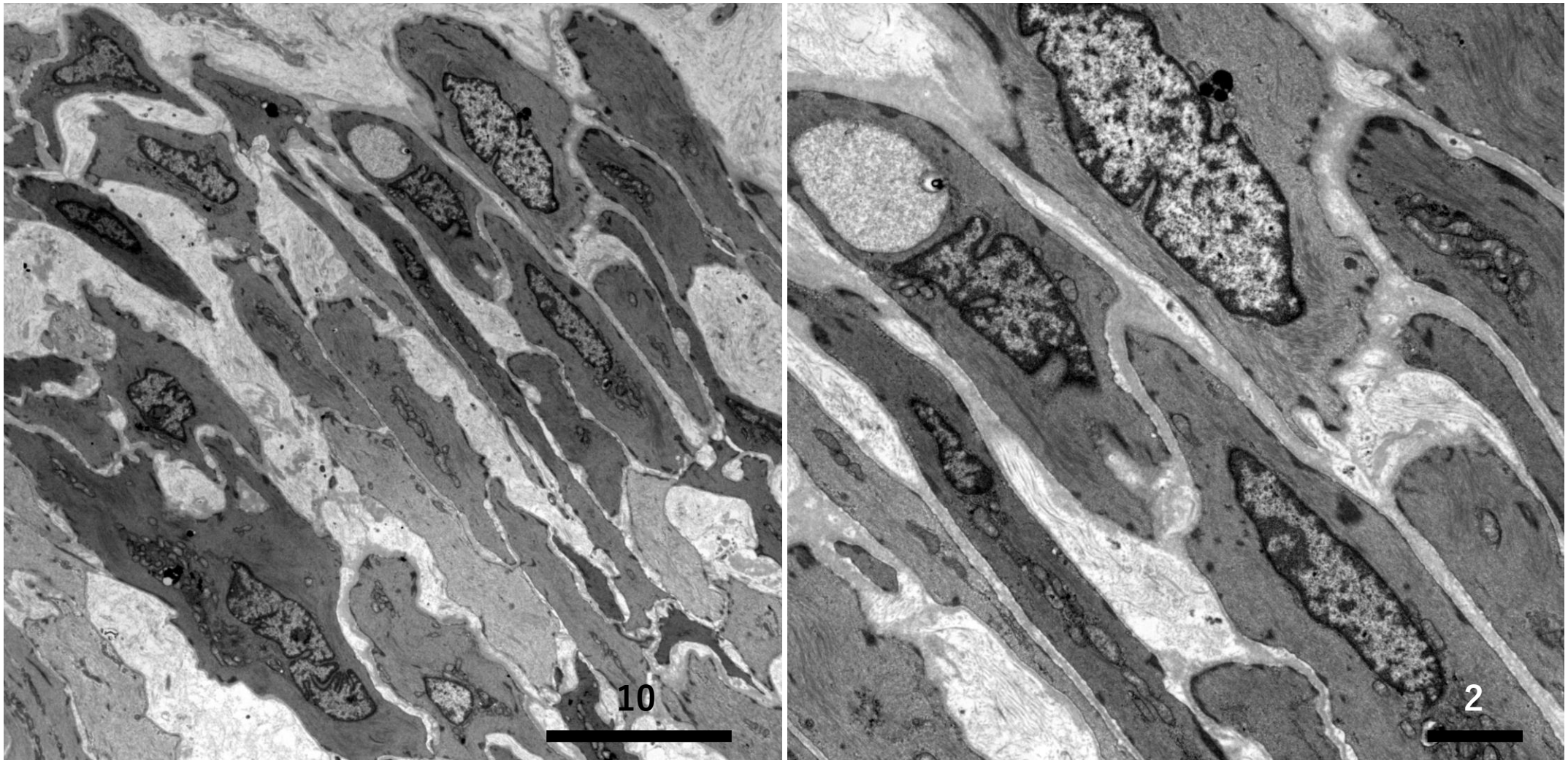
Skin biopsy taken from a 59 y-o female patient clinically suspected of neuroferritinopathy with a family history. No abnormality is discerned in the capillary vessels, an arteriole and subcutaneous fat cells at the light microscopic level (H&E-3).



Ultrastructure of the subcutaneous fat cell in the skin biopsy taken from a 59 y-o female patient clinically suspected of neuroferritinopathy with a family history. In the cytoplasm of the mature fat cell, small vacuoles are observed (EM-1)



Ultrastructure of the arteriole in the skin biopsy taken from a 59 y-o female patient clinically suspected of neuroferritinopathy with a family history. In the cytoplasm of the arteriolar endothelial cells, large-sized vacuoles containing amorphous floccular substances are observed (EM-2)



Ultrastructure of the medial smooth muscles of the arteriole in the skin biopsy taken from a 59 y-o female patient clinically suspected of neuroferritinopathy with a family history. In the cytoplasm of the arteriolar smooth muscle cells, formation of a large vacuole containing amorphous floccular substances is observed (EM-3)