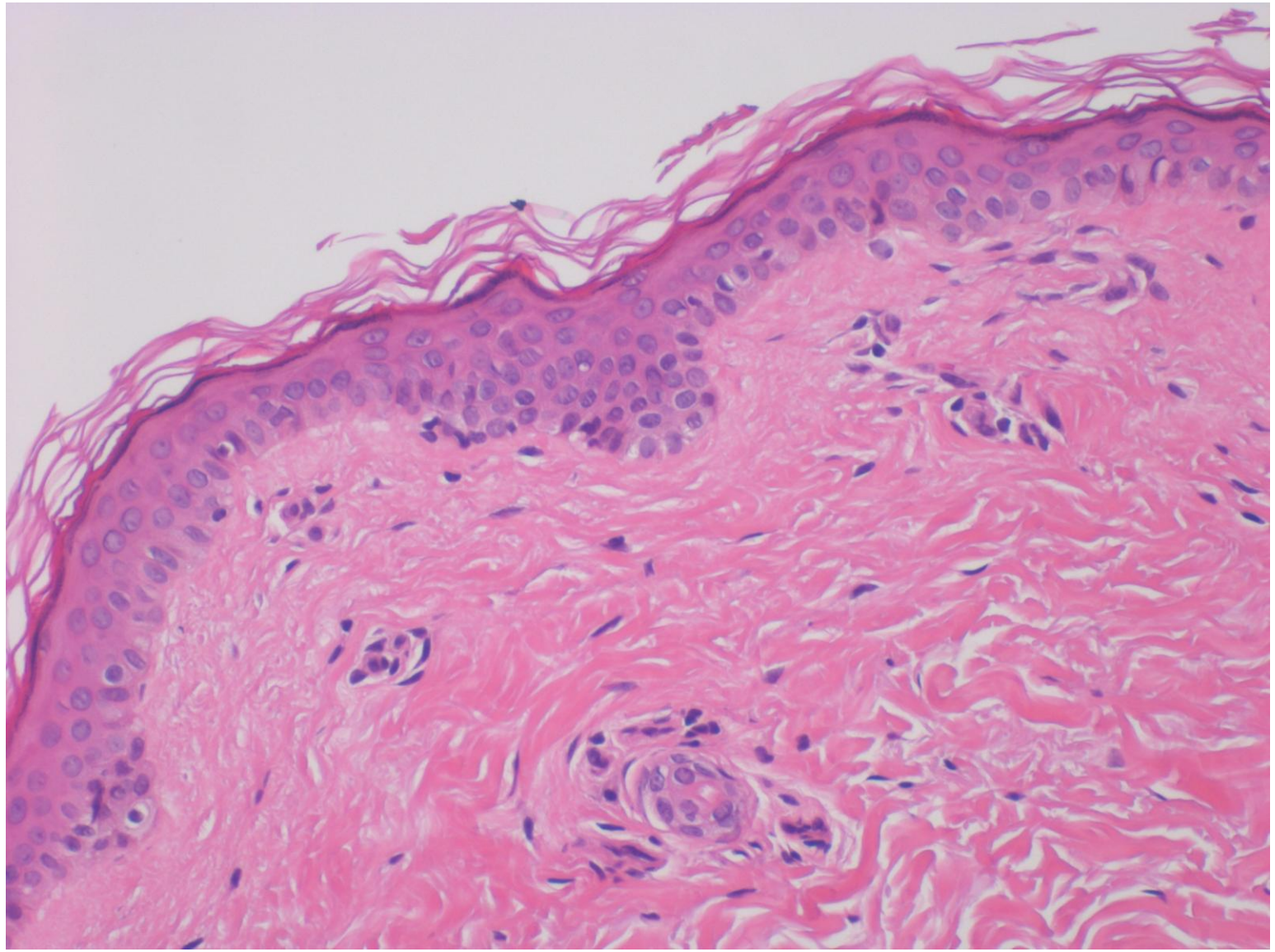
Four progressive neuronal disorders ultrastructurally diagnosed with skin biopsy preparations

1) CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
2) neuronal intranuclear hyaline inclusion disease (NIHID)
3) neuronal ceroid lipofuscinosis
4) Lafora disease

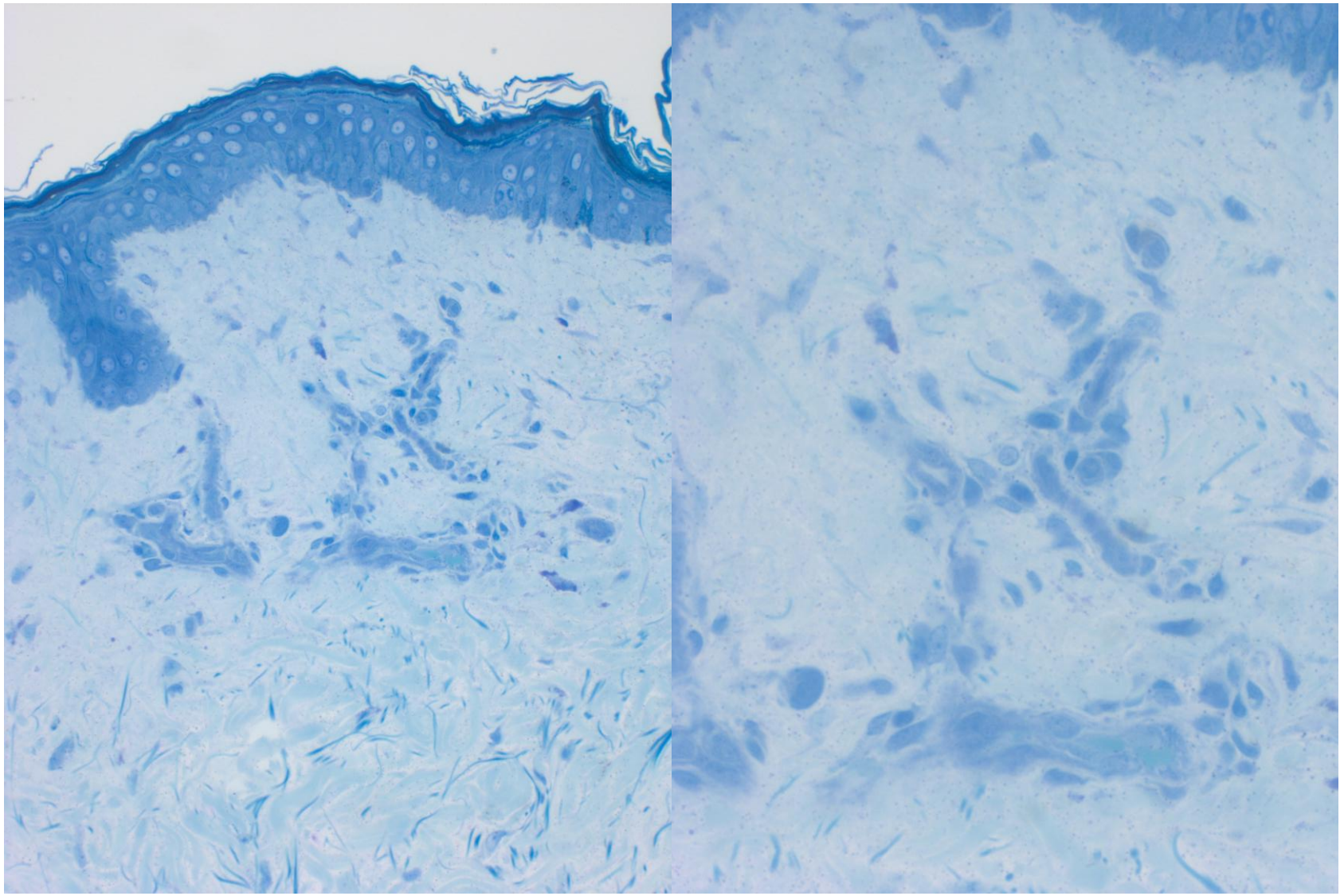
In Parkinson's disease, phosphorylated α-synuclein-positive dot-like inclusion bodies are observed in the peripheral autonomic nerve fibers (figures not shown).

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

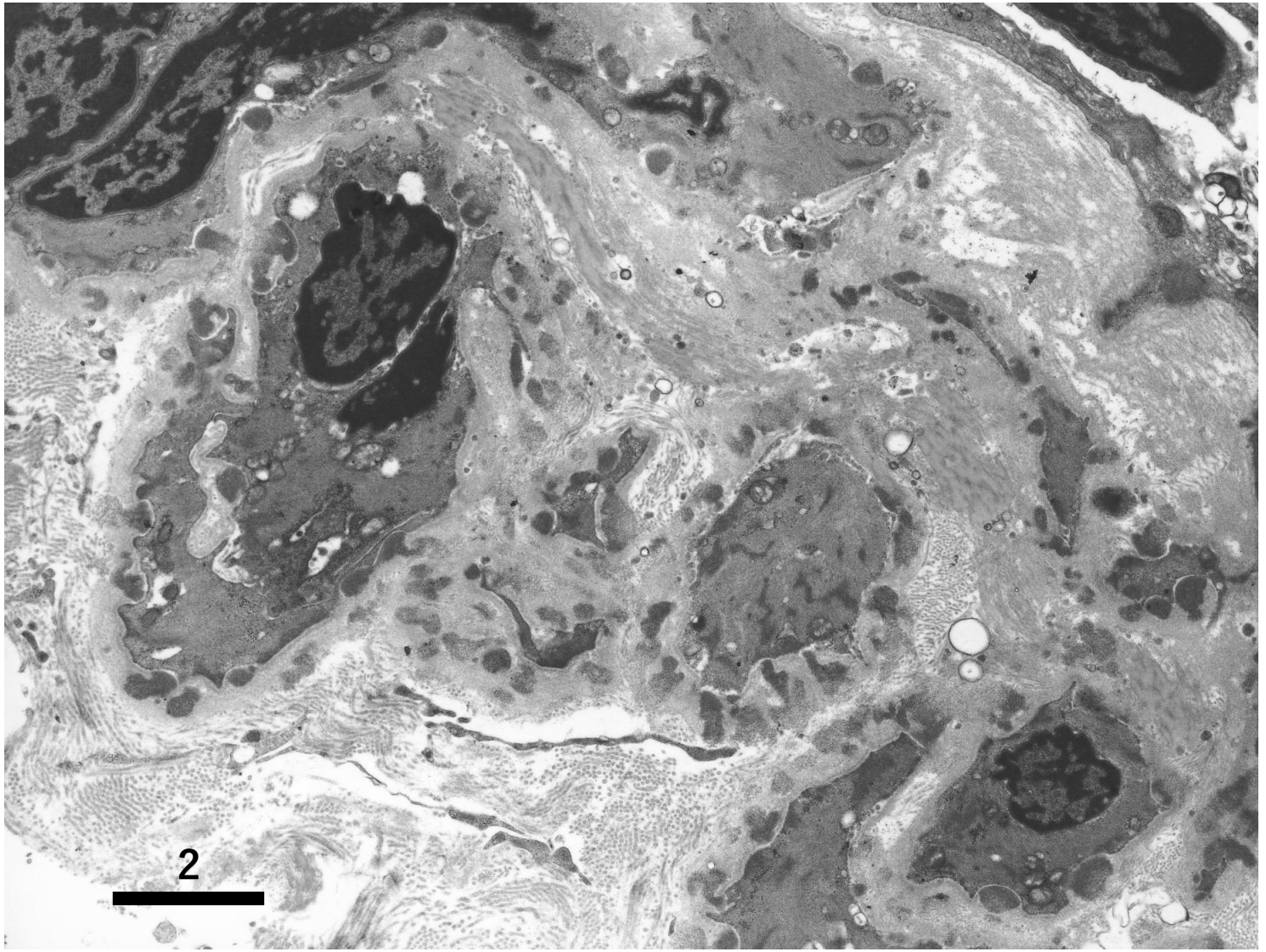
CADASIL is a rare autosomal dominant inherited disorder caused by a mutation in the Notch3 gene. The thickening of the wall of small- and medium-sized blood vessels in the white matter blocks the flow of blood to the brain. Symptoms include headache, strokes, seizures, vision problems, parkinsonism, apathy and depression. The disease progresses slowly. By age 65, most individuals with CADASIL have cognitive problems and dementia. Electron microscopic study of the skin biopsy specimen is quite useful to confirm the diagnosis.



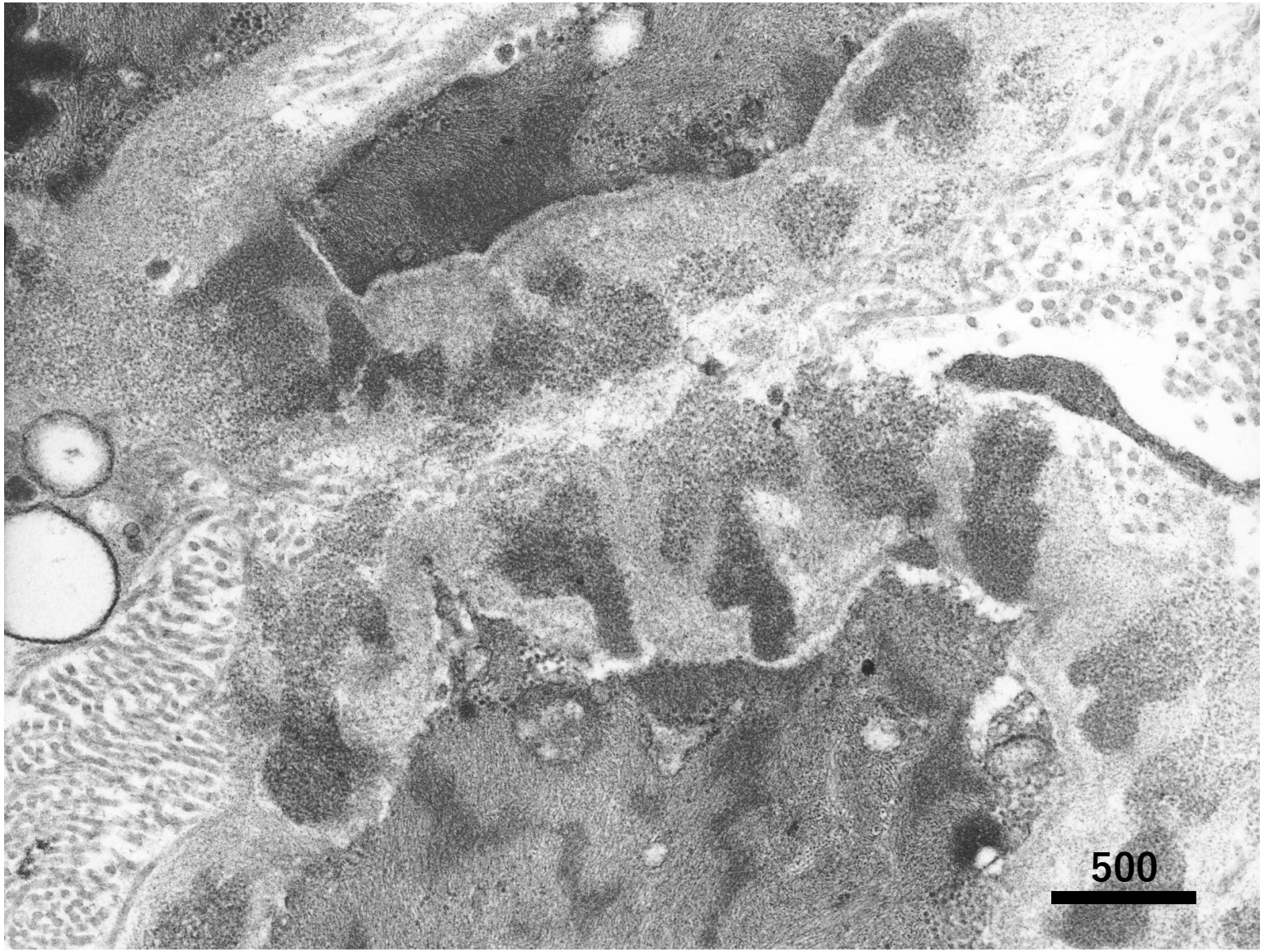
H&E–stained skin biopsy specimen from a CADASIL patient (45 y-o male) appears to be normal.



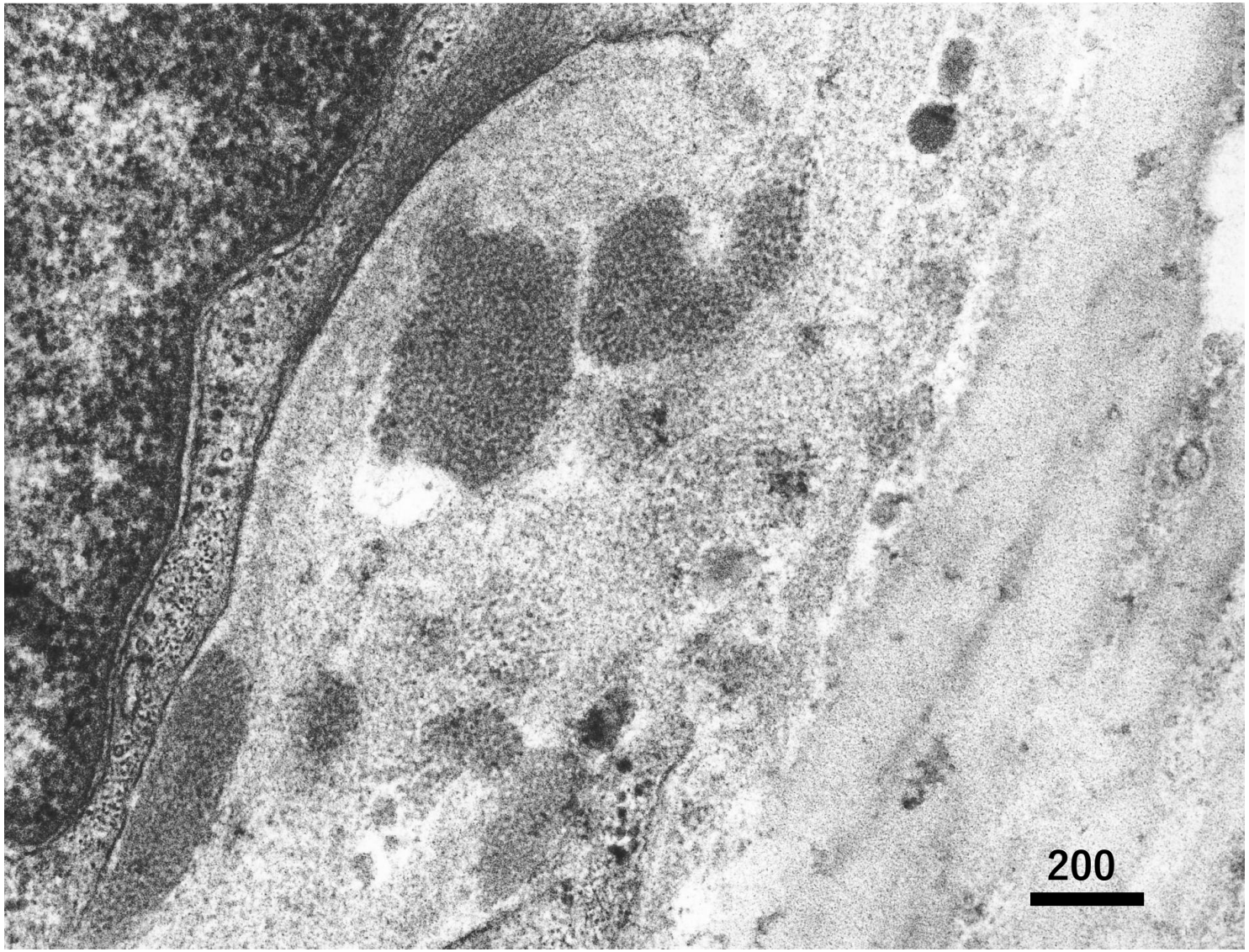
Toluidine blue–stained semithin sections of the skin biopsy specimen biopsied from a CADASIL patient (45 Y-O MALE) appears to be normal. Light microscopically, No abnormality is recognizable in the capillary wall.



EM-1: Electron microscopically, electron dense material, so-called granular osmiophilic material (GOM), is evident beneath the capillary endothelial cells.



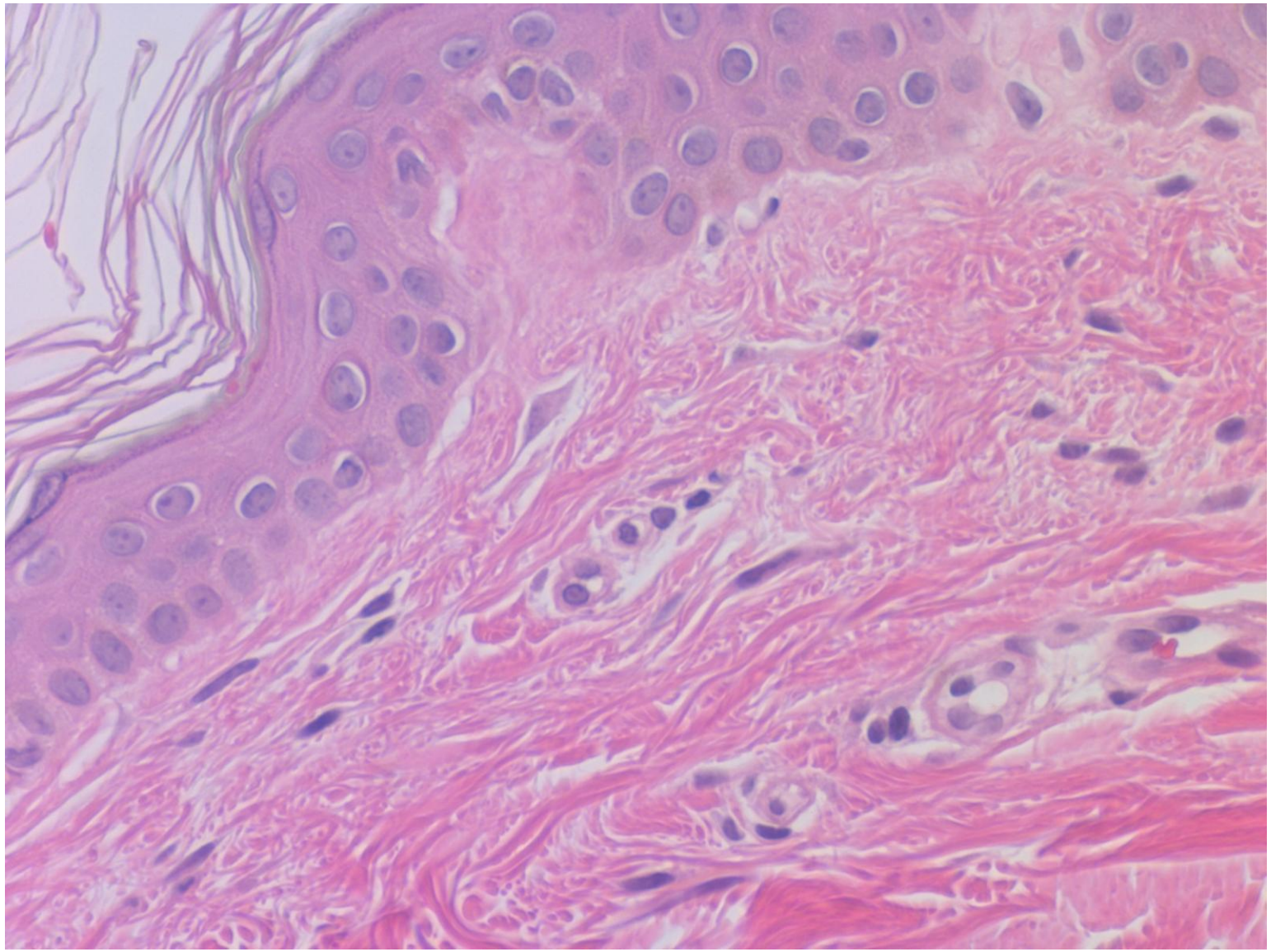
EM-2: Electron microscopically, electron dense material, so-called granular osmiophilic material (GOM), is evident beneath the capillary endothelial cells.



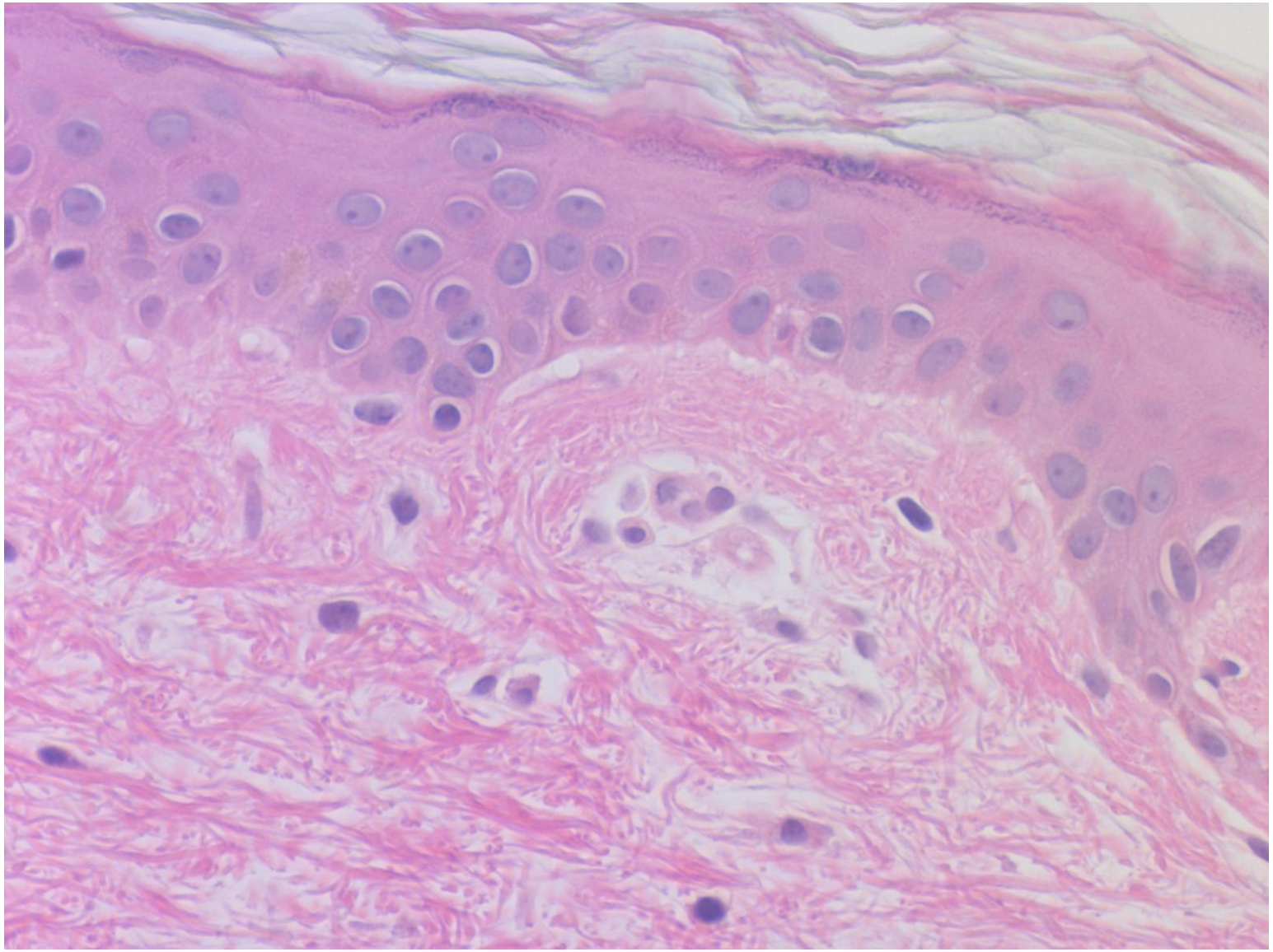
EM-3: Electron microscopically, electron dense material, so-called granular osmiophilic material (GOM), is evident beneath the capillary endothelial cells.

neuronal intranuclear hyaline inclusion disease (NIHID)

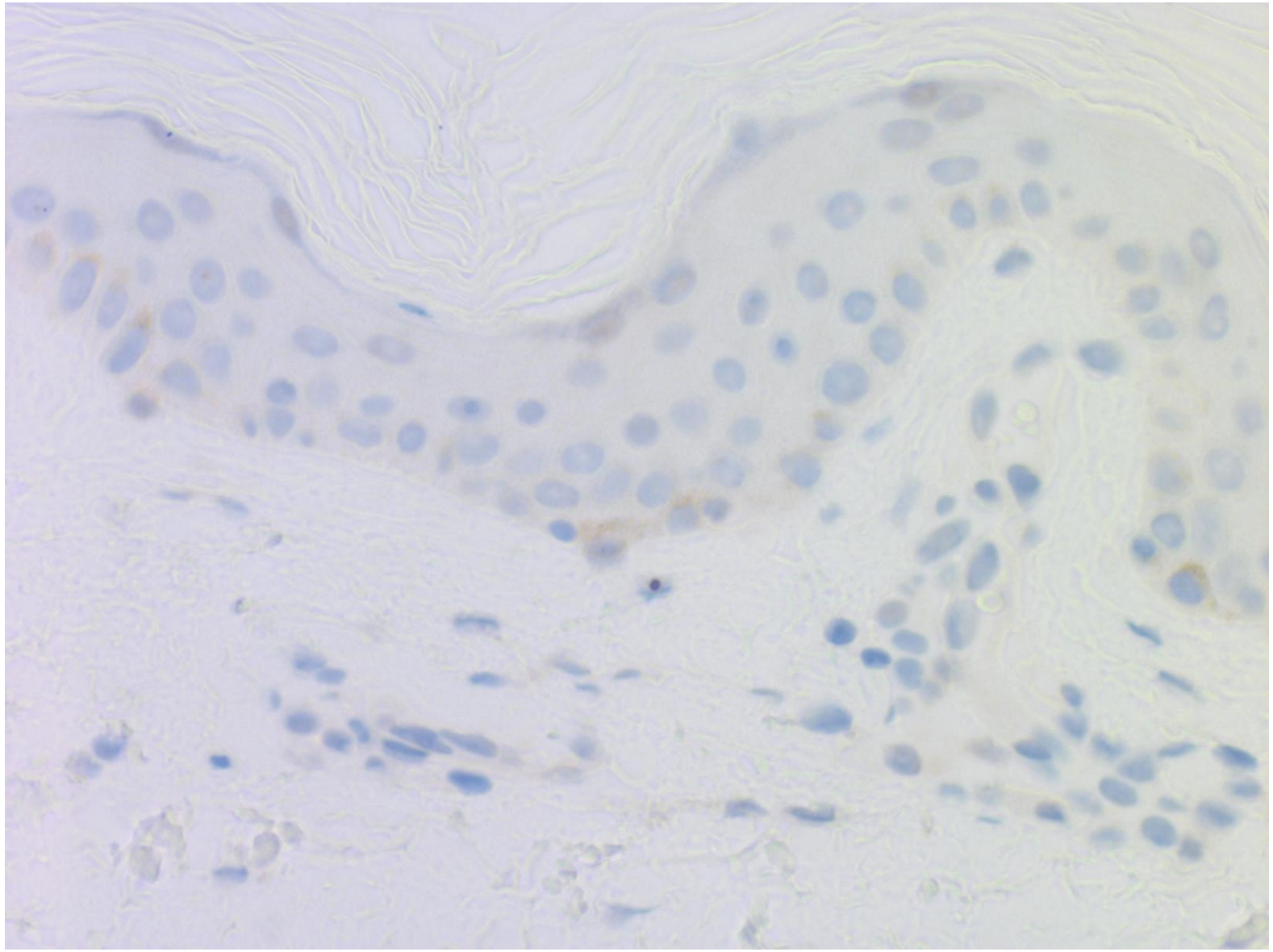
Neuronal intranuclear hyaline inclusion disease (NIHID) is a rare neurodegenerative disorder pathologically characterized by localized neuronal loss and the presence of ubiquitin-immunoreactive eosinophilic intranuclear inclusions in neurons and glial cells. The glial cell involvement leads to severe white matter degradation (leukoencephalopathy). The disease is subdivided into three clinical groups: infantile, juvenile and adult forms. Main symptoms of the adult-onset type are progressive cognitive dysfunction. The disease is caused by the elongation of GGC repeats on NOTCH2NLC gene. Skin biopsy is quite useful to confirm the diagnosis.



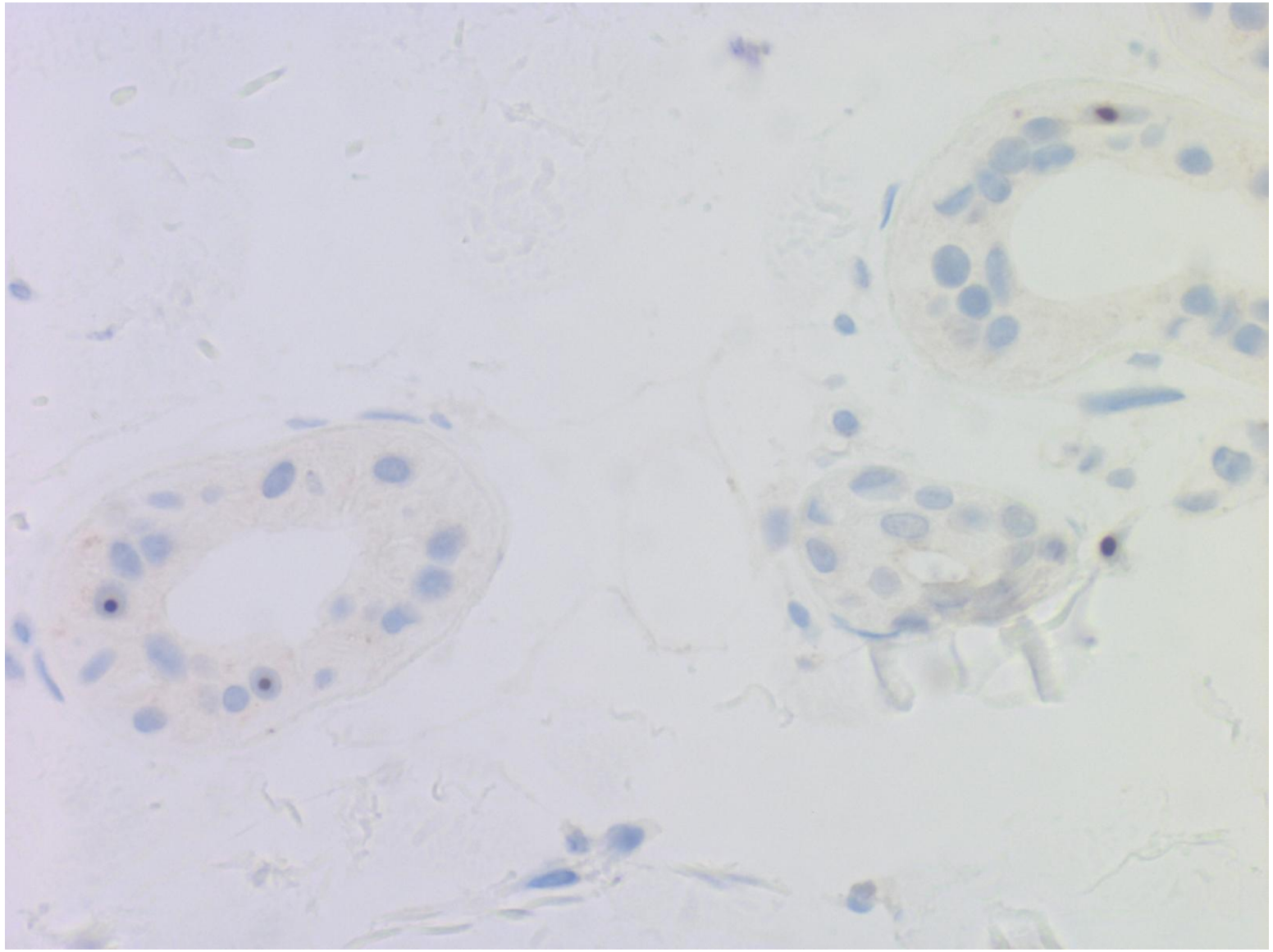
Skin biopsy from a 68 year-old female patient with neuronal intranuclear hyaline inclusion disease (NIHID) is shown. No abnormality is observed light microscopically. H&E-1



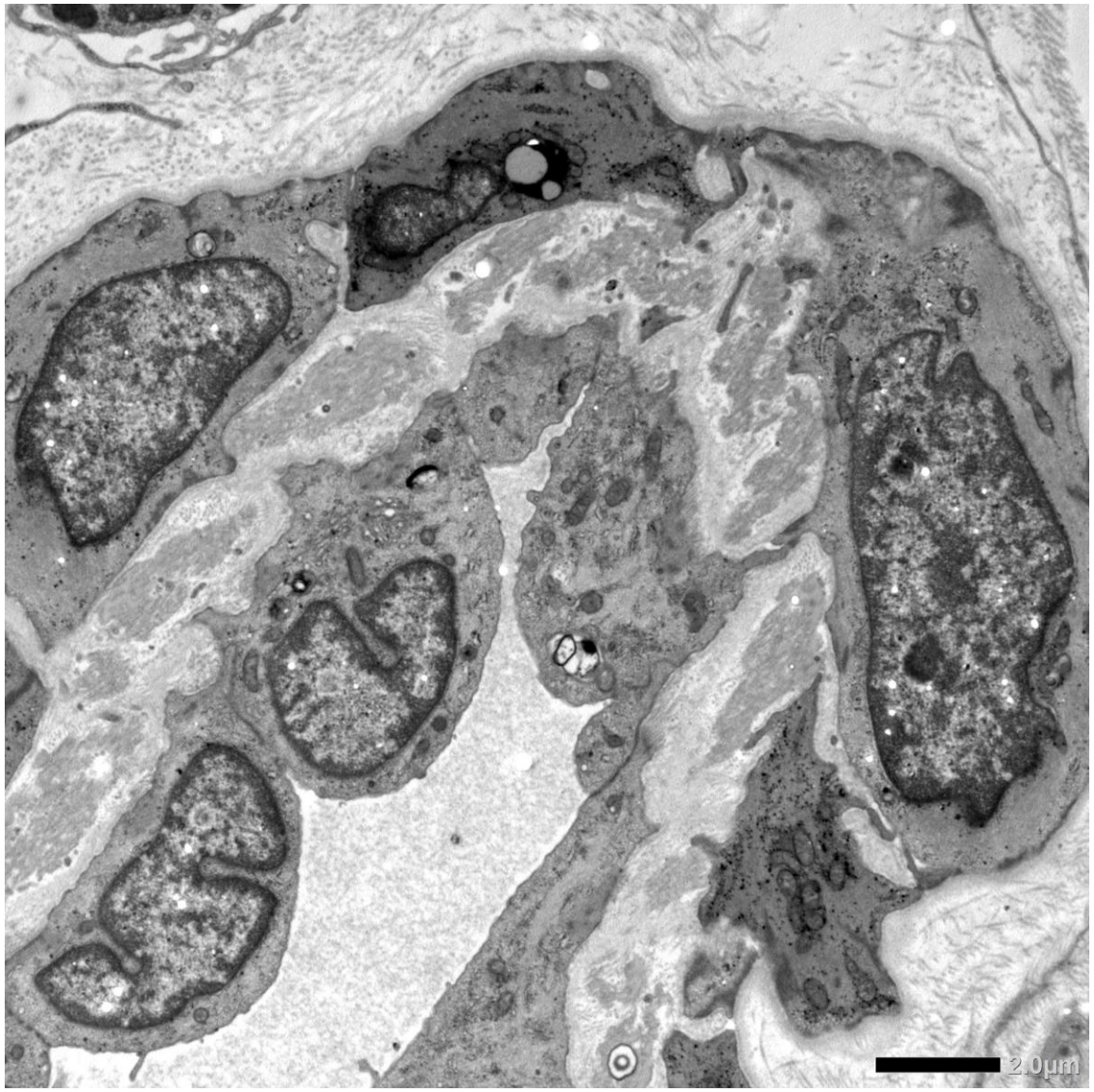
Skin biopsy from a 68 year-old female patient with neuronal intranuclear hyaline inclusion disease (NIHID) is shown. No abnormality is observed light microscopically. H&E-2



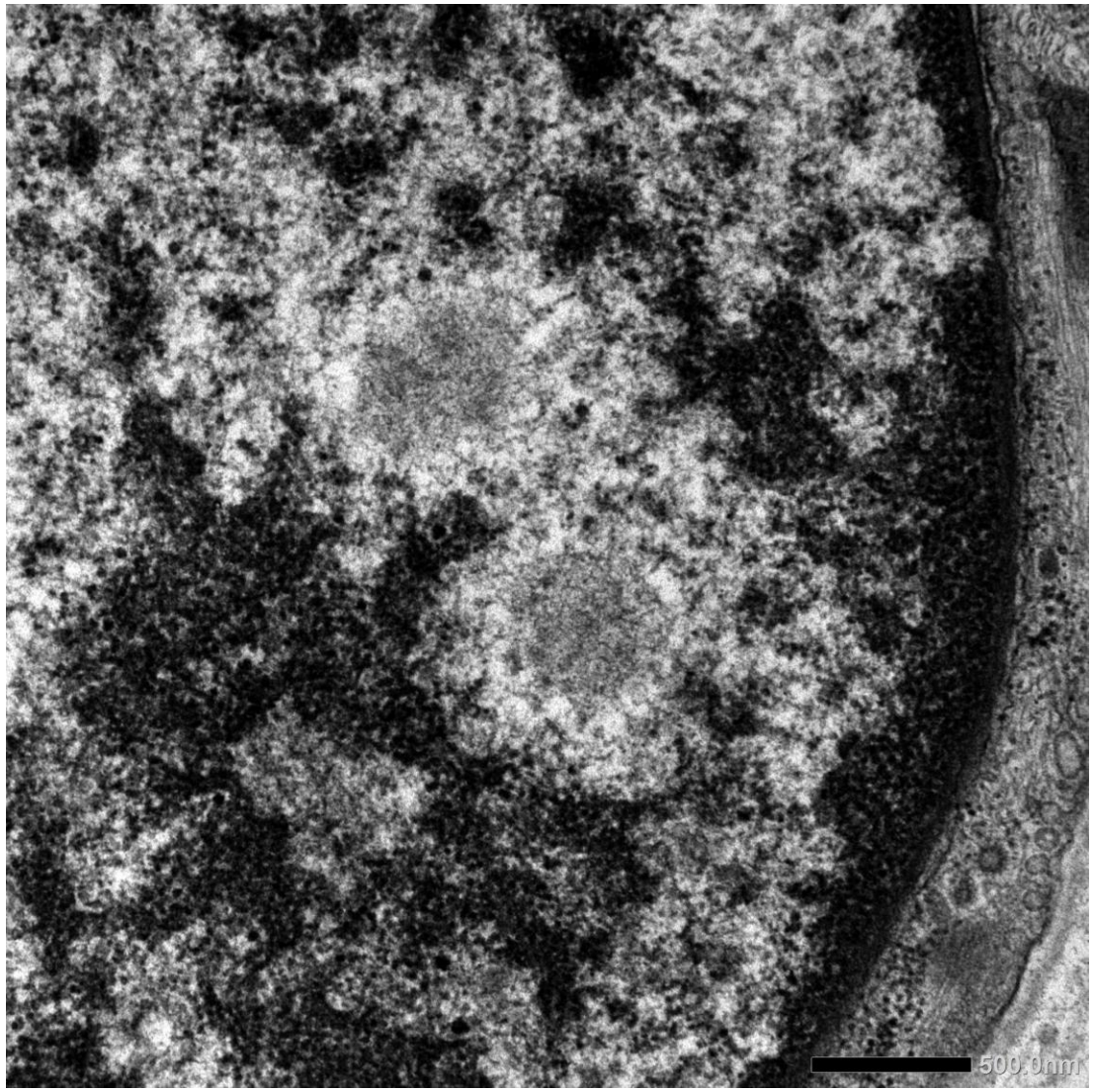
Skin biopsy from a 68 year-old female patient with neuronal intranuclear hyaline inclusion disease (NIHID) reveals ubiquitin-positive intranuclear inclusion bodies in a few fibroblastic cells. The inclusions are also positive for p62. Ubiquitin immunostaining-1



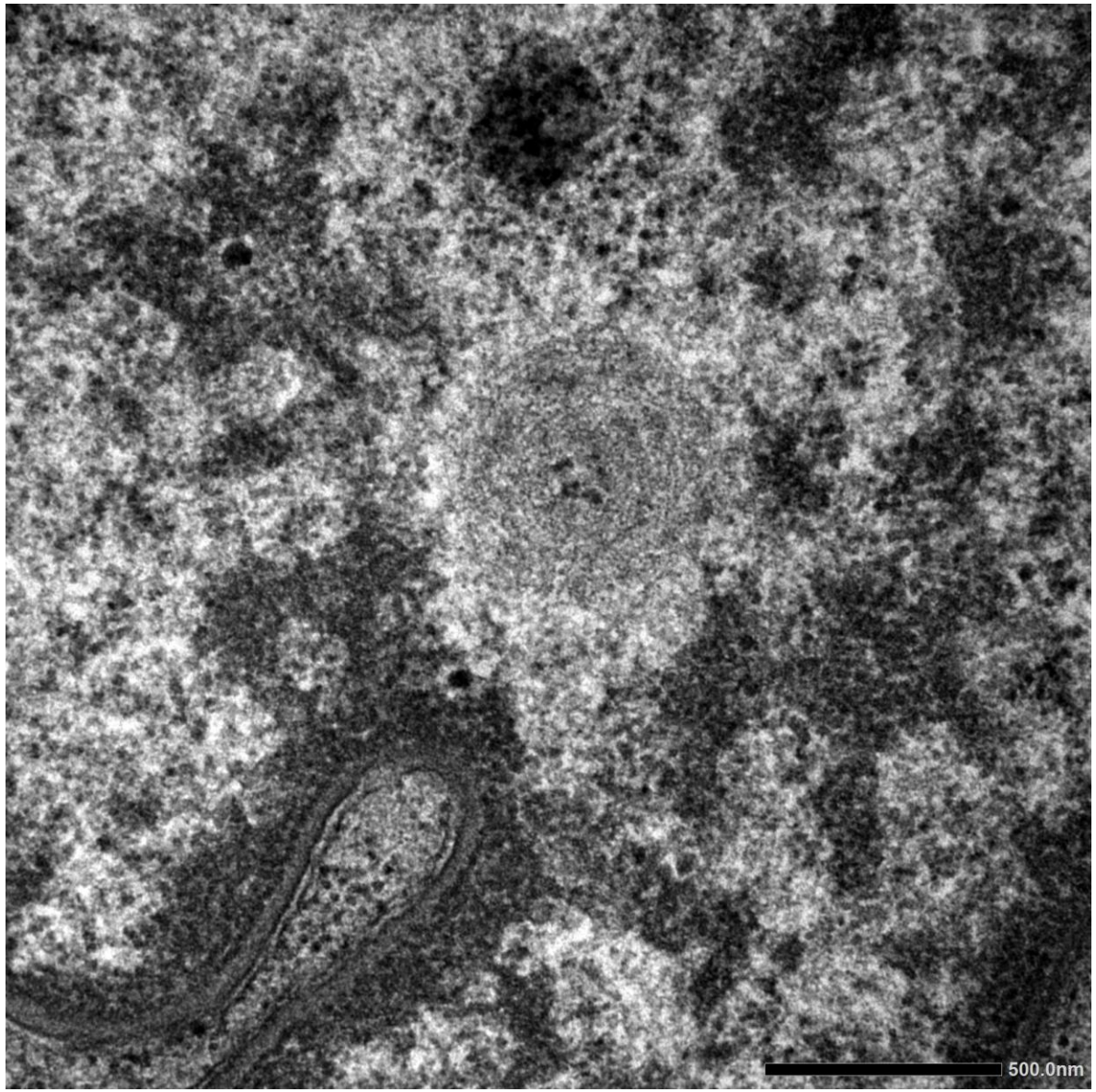
Skin biopsy from a 68 year-old female patient with neuronal intranuclear hyaline inclusion disease (NIHID) reveals ubiquitin-positive intranuclear inclusion bodies in a few sweat gland ductal cells and fibroblastic cells. The inclusions are also positive for p62. Ubiquitin immunostaining-2



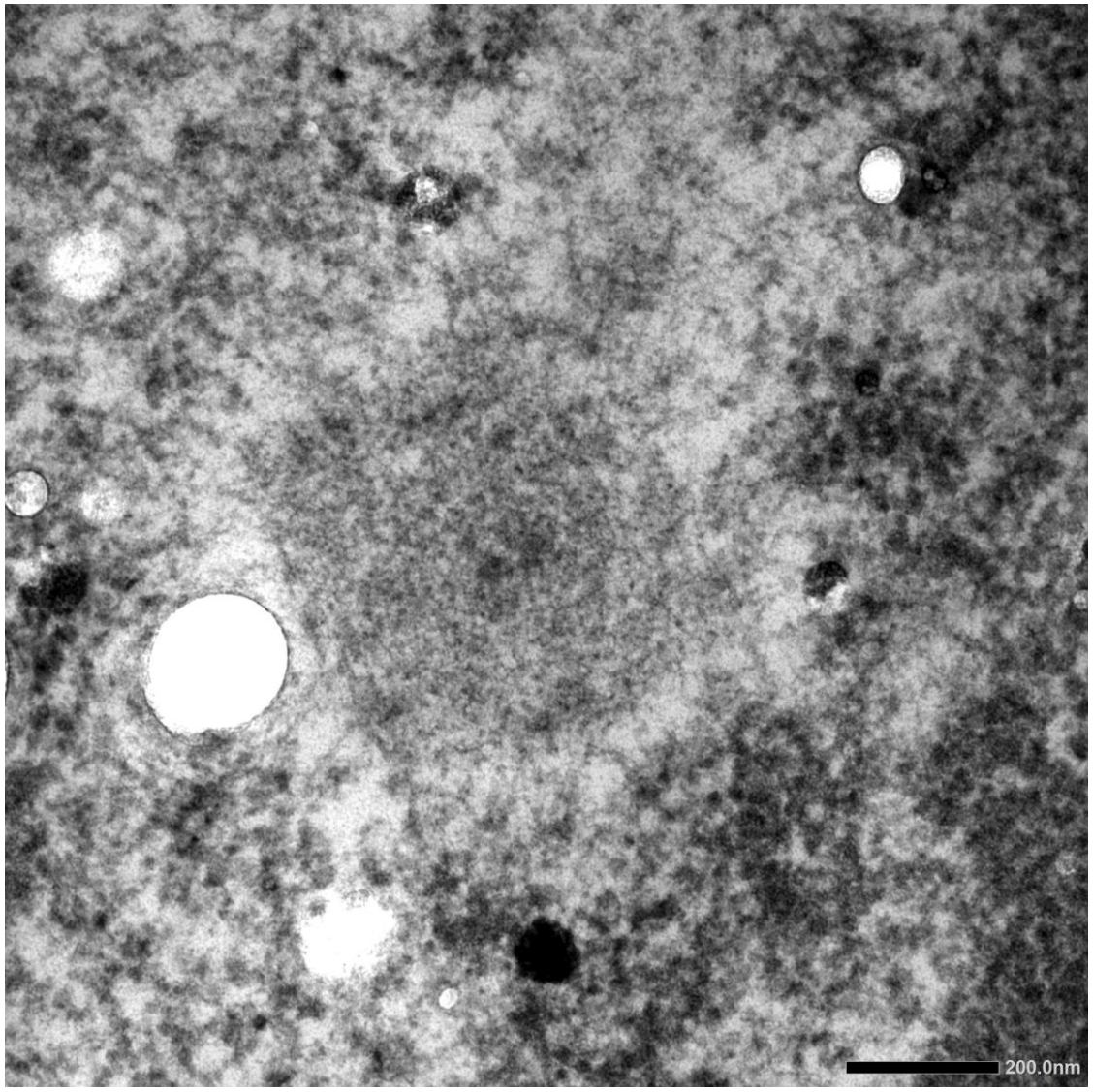
Ultrastructurally, small intranuclear inclusion bodies are observed in capillary endothelial cells. EM-1



Ultrastructurally, small intranuclear inclusion bodies are observed in capillary endothelial cells. The size of the filamentous intranuclear inclusion bodies range from 300 to 700 nm. EM-2



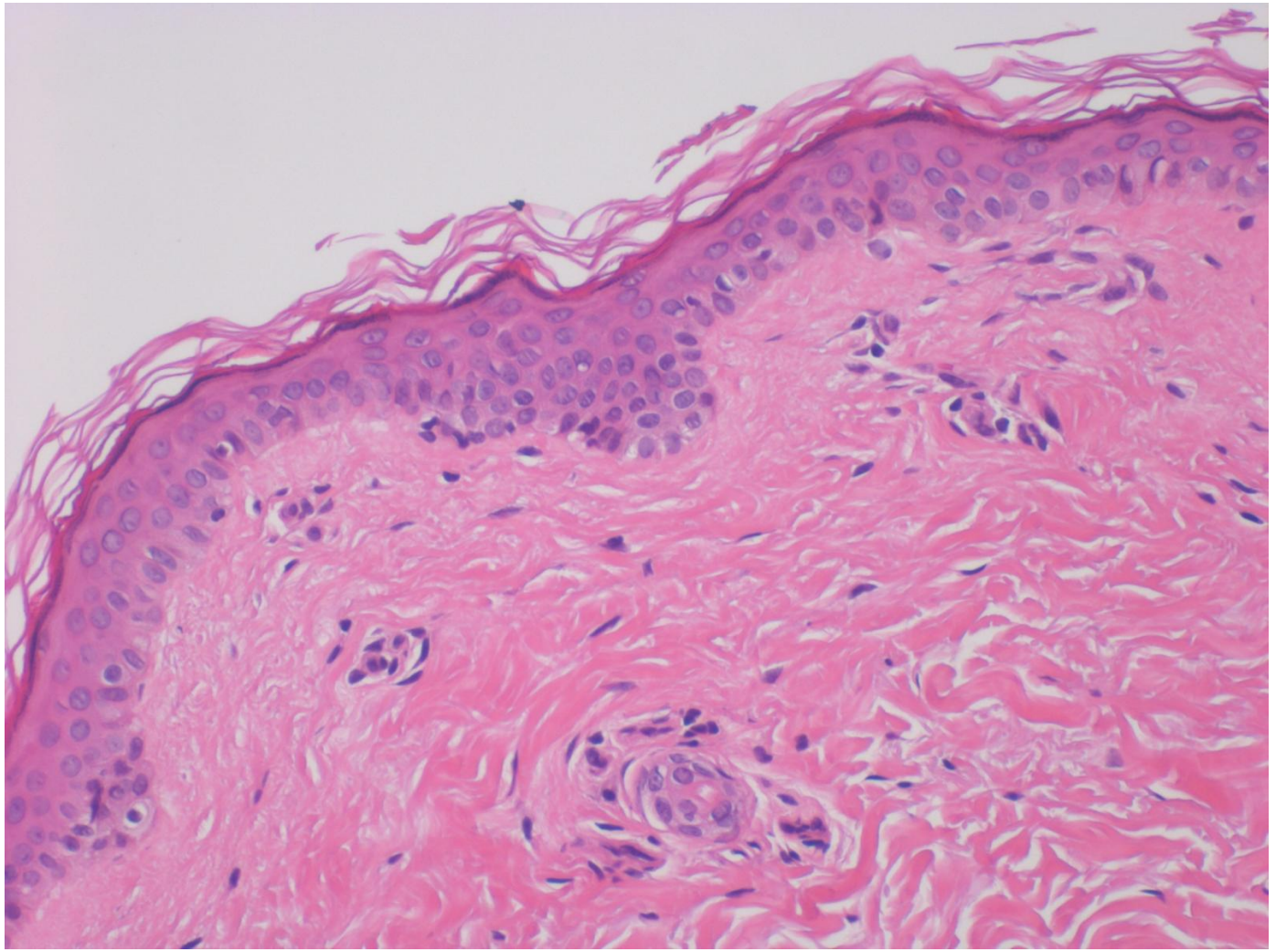
Ultrastructurally, small intranuclear inclusion bodies are observed in capillary endothelial cells. The size of the filamentous intranuclear inclusion bodies range from 300 to 700 nm. EM-3



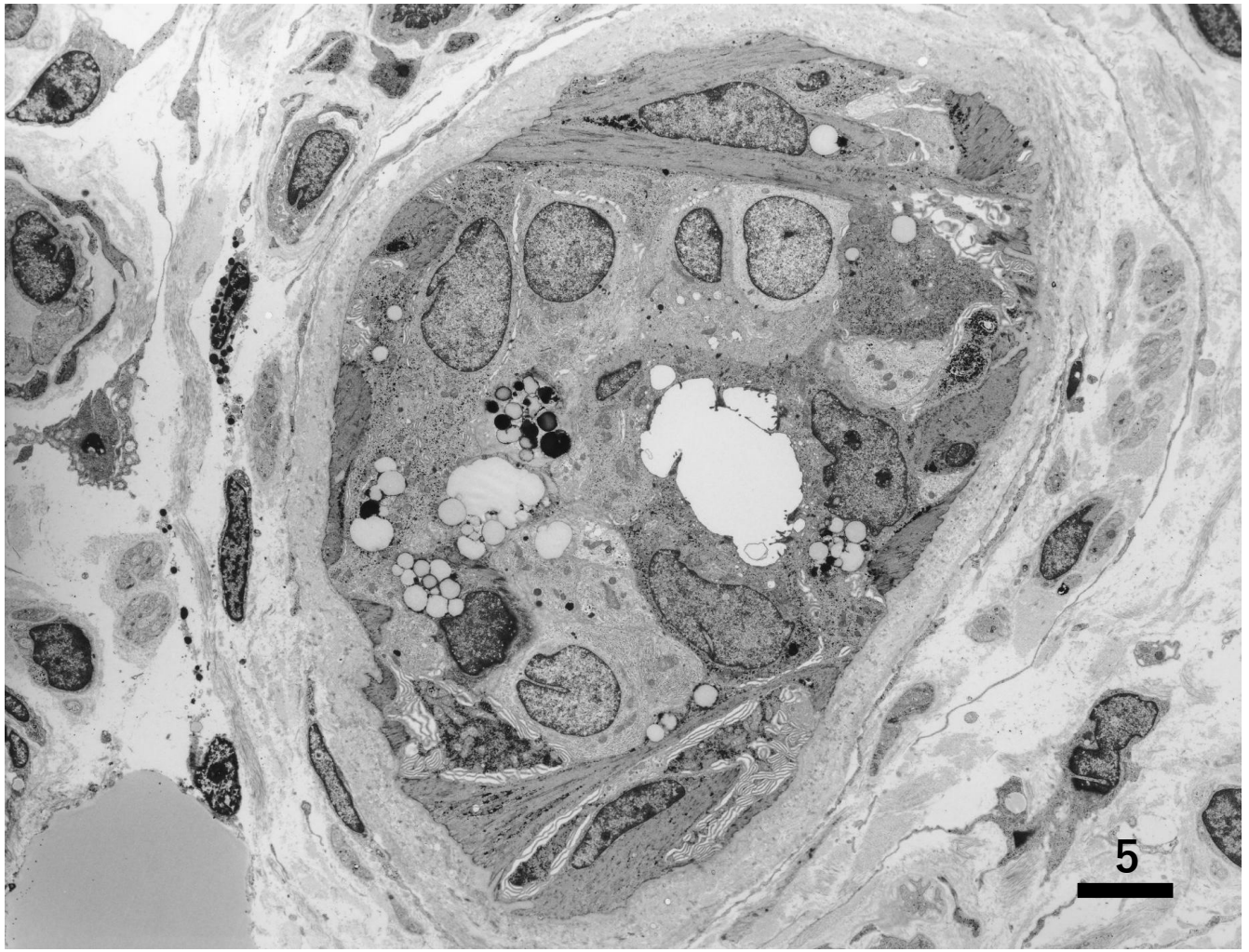
Ultrastructurally, small intranuclear inclusion bodies are observed in capillary endothelial cells. The size of the filamentous intranuclear inclusion bodies range from 300 to 700 nm. EM-4

neuronal ceroid lipofuscinosis

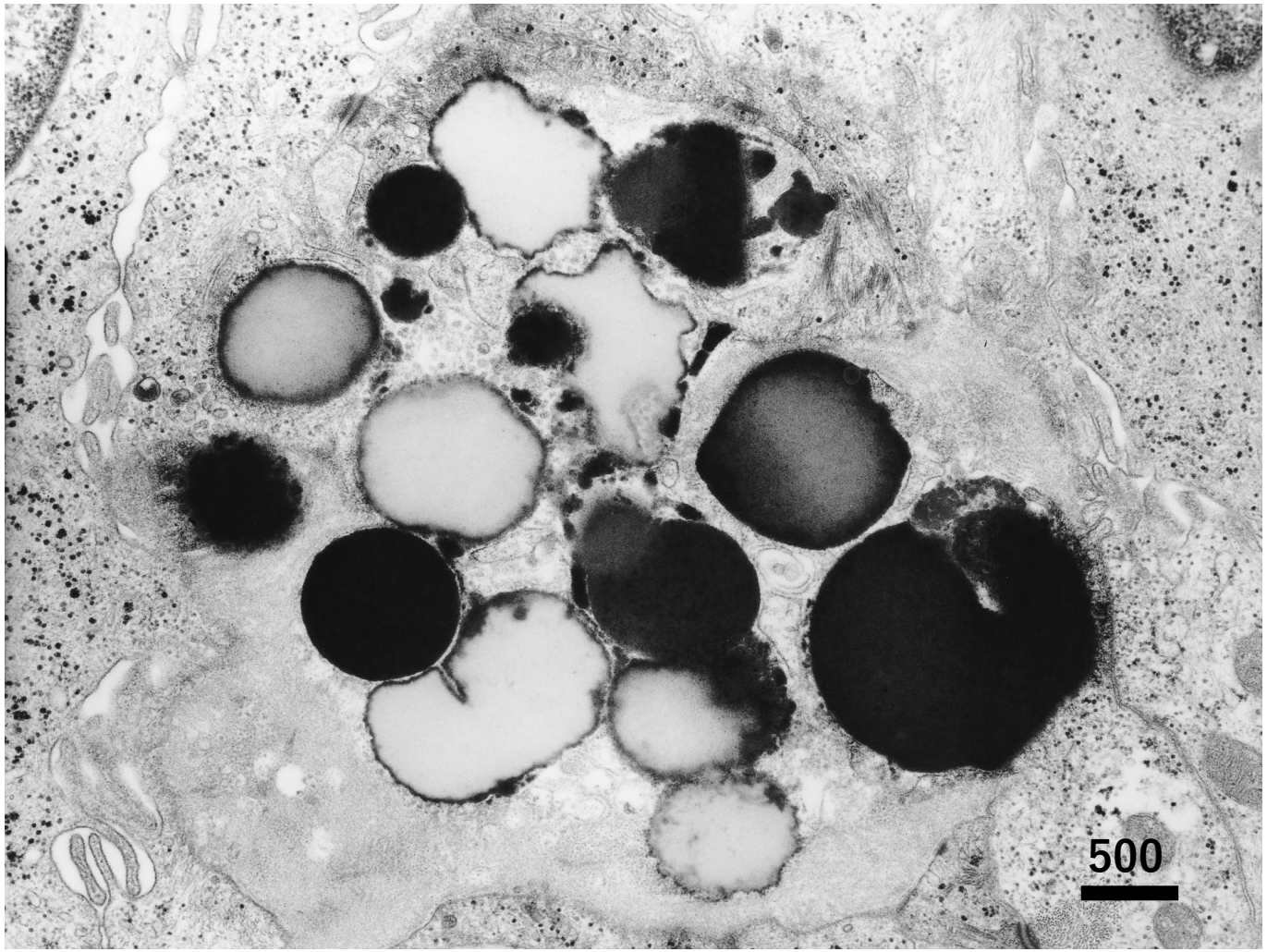
Neuronal ceroid lipofuscinosis (Batten disease) is an inherited progressive degenerative brain disorder, most often manifesting in childhood. The disease is featured by a decline of mental capacity, epilepsy and vision disturbance. Microscopically, intracellular accumulation of an autofluorescent material, ceroid lipofuscin is seen in neurons in the brain and retina. Ultrastructural study of the skin biopsy specimen is used for confirming the diagnosis.



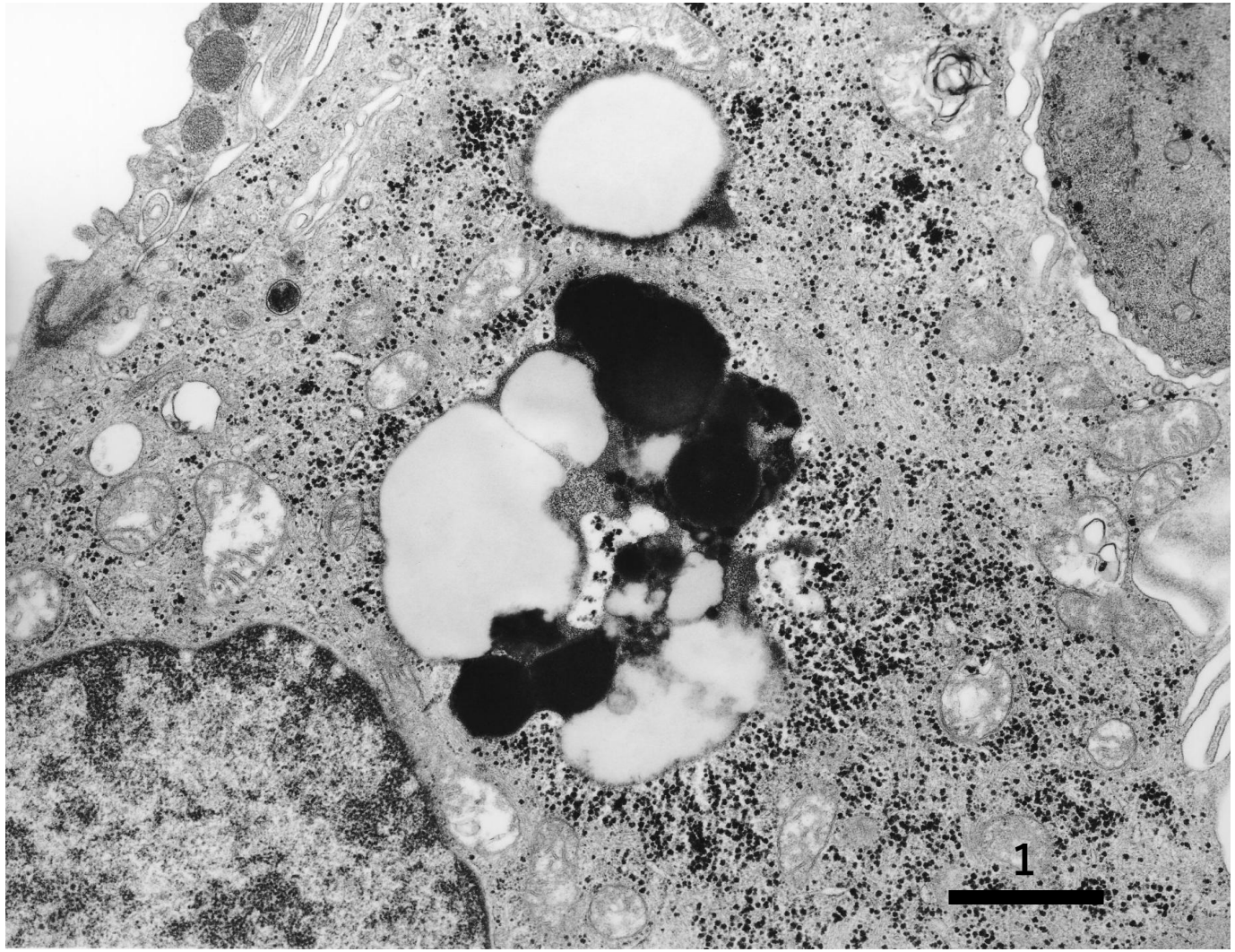
Skin biopsy was performed from a 60-year-old male patient with neuronal ceroid lipofuscinosis (Batten disease). Progressive dementia started 6 years earlier. MRI reveals diffuse periventricular leukoencephalopathy. No light microscopic abnormality is recognized in H&E preparation of the skin.



Ultrastructurally, lipidic cytoplasmic inclusions are seen in the duct-lining cells of the eccrine sweat gland. EM-1



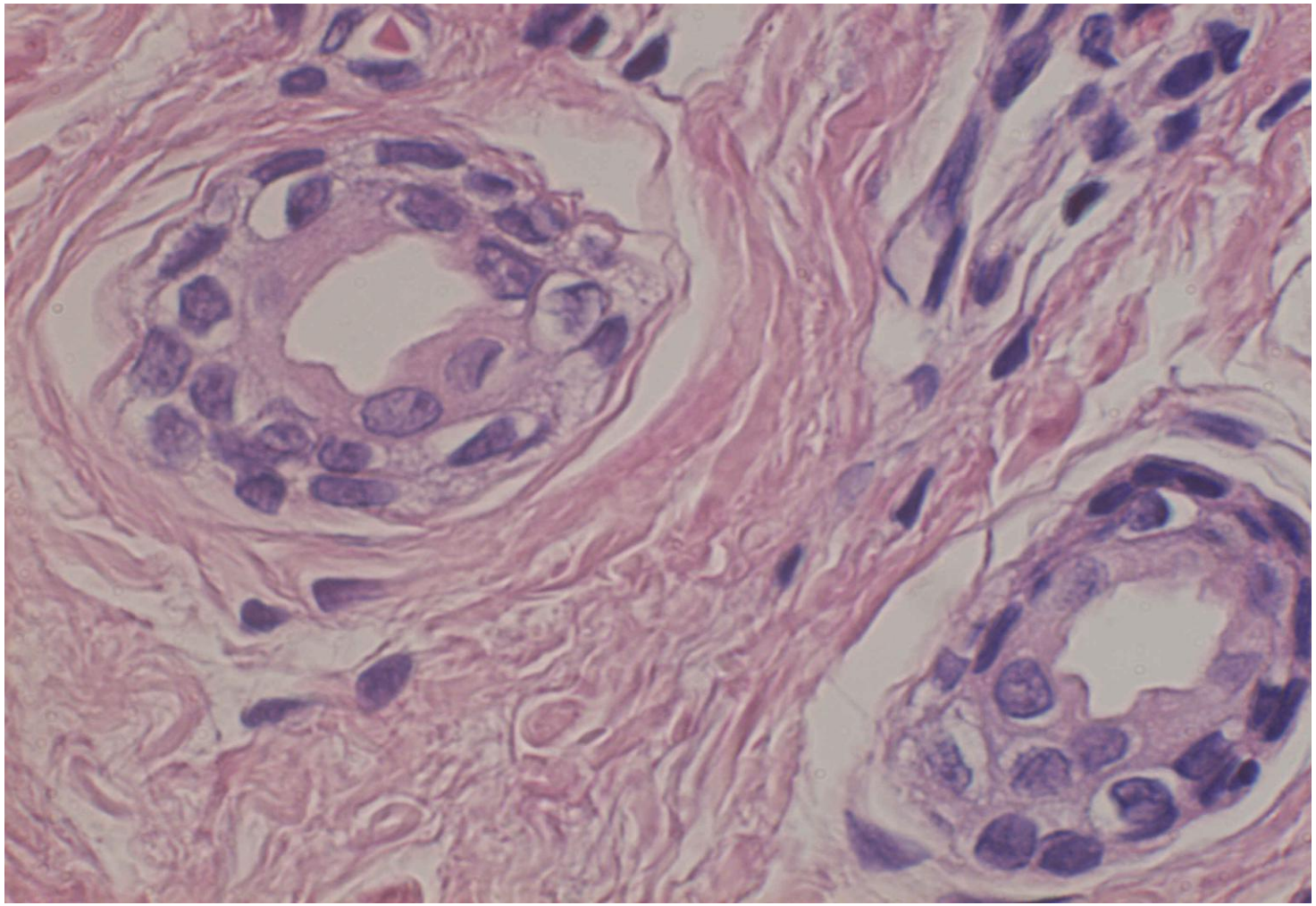
Ultrastructurally, lipidic cytoplasmic inclusions are seen in the duct-lining cells of the eccrine sweat gland. Clusters of lipid droplets are closely associated with ceroid/lipofuscin-like electron-dense material. EM-2



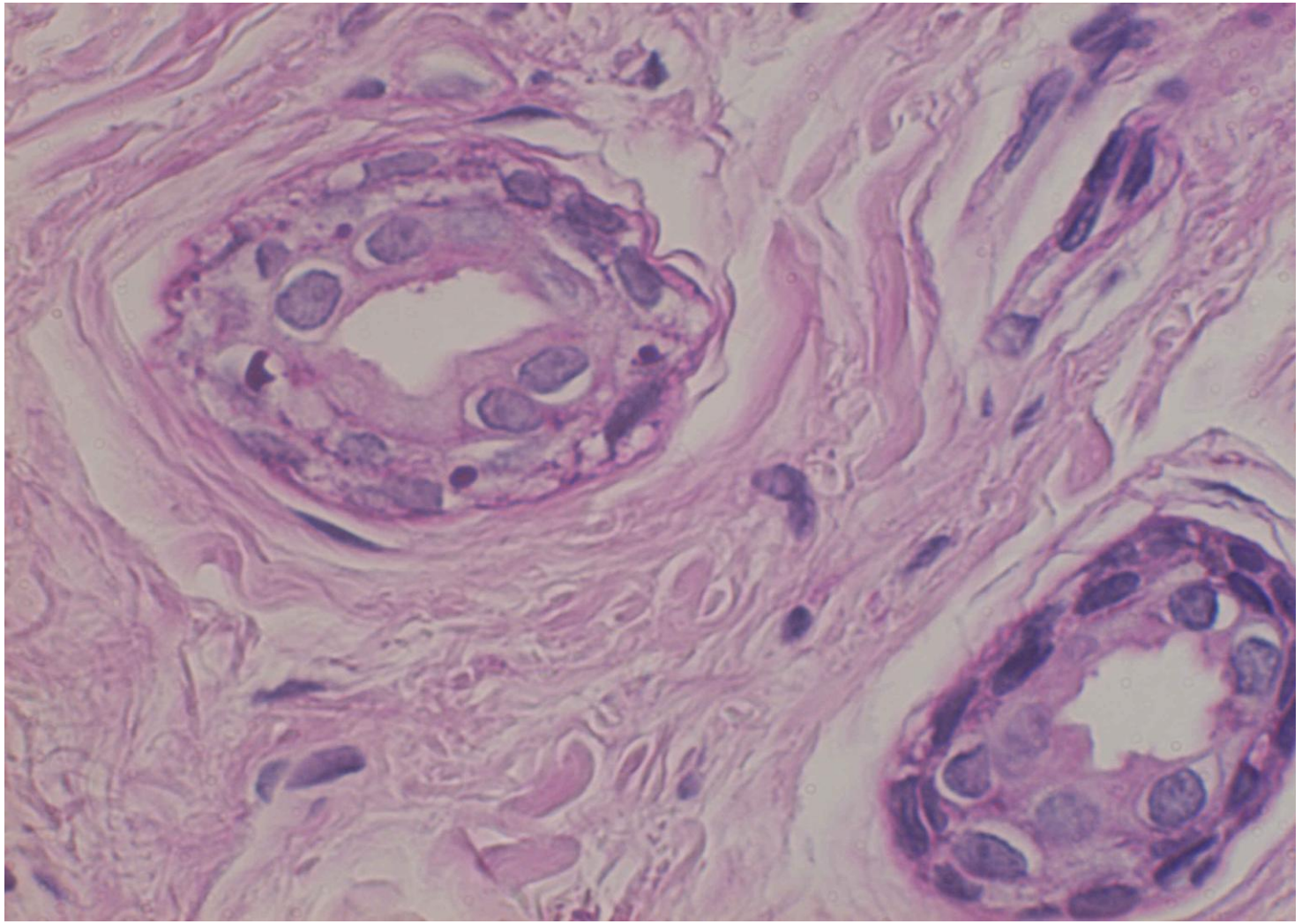
Ultrastructurally, lipidic cytoplasmic inclusions are seen in the duct-lining cells of the eccrine sweat gland. Clusters of lipid droplets are closely associated with ceroid/lipofuscin-like electron-dense material. EM-3

Lafora disease

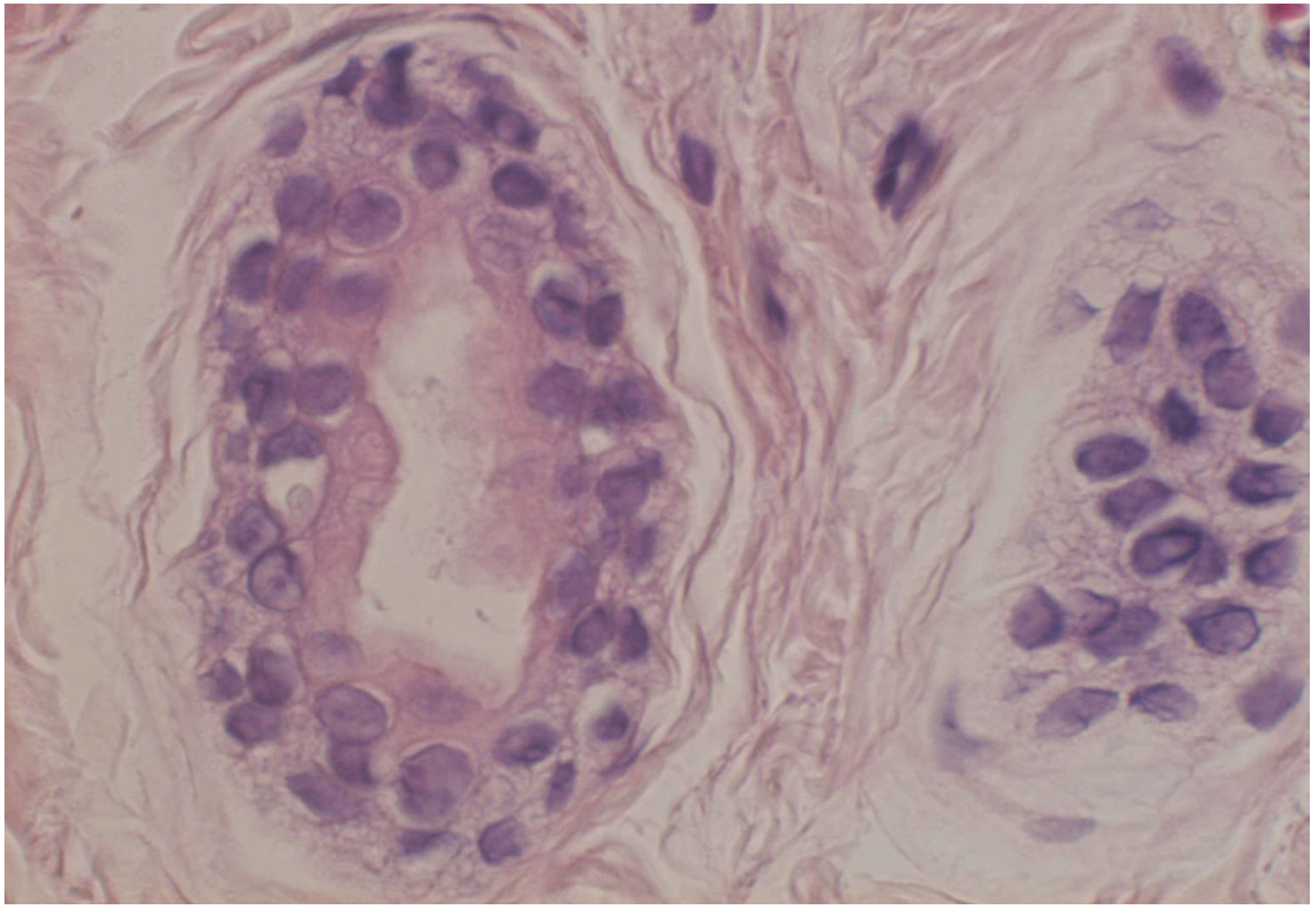
Lafora disease is an autosomal recessive, progressive myoclonus epilepsy with cerebellar palsy and intellectual disability. The disease usually manifests in adolescence, and death commonly occurs within 10 years of symptom onset. The disease is caused by loss-of-function mutations in EPM2A or NHLRC1, encoding laforin and malin, respectively. The lack of the proteins results in poorly branched, hyperphosphorylated glycogen with long glucose chains (polyglucosamines), precipitating into PAS-positive Lafora bodies. Intracellular cytoplasmic inclusions lead to neurodegeneration. Skin biopsy reveals deposition of PAS-positive cytoplasmic inclusions (round or crescentic in shape) in the myoepithelial cells of the sweat gland.



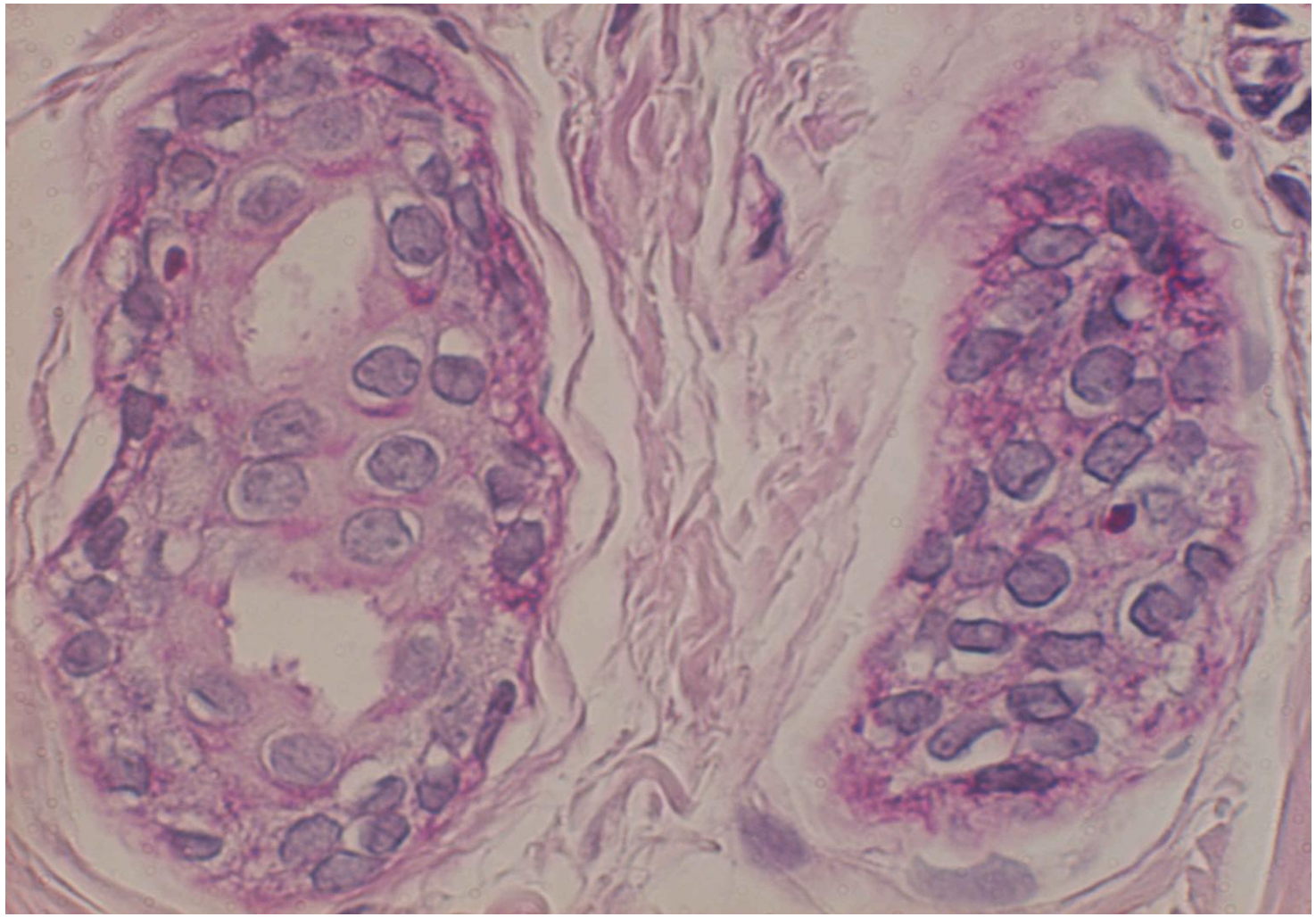
Skin biopsy from a 16-year-old boy (onset at 13 years old) shows unremarkable histology. The eccrine sweat gland ducts are shown. No inclusion bodies are recognizable.
H&E-1



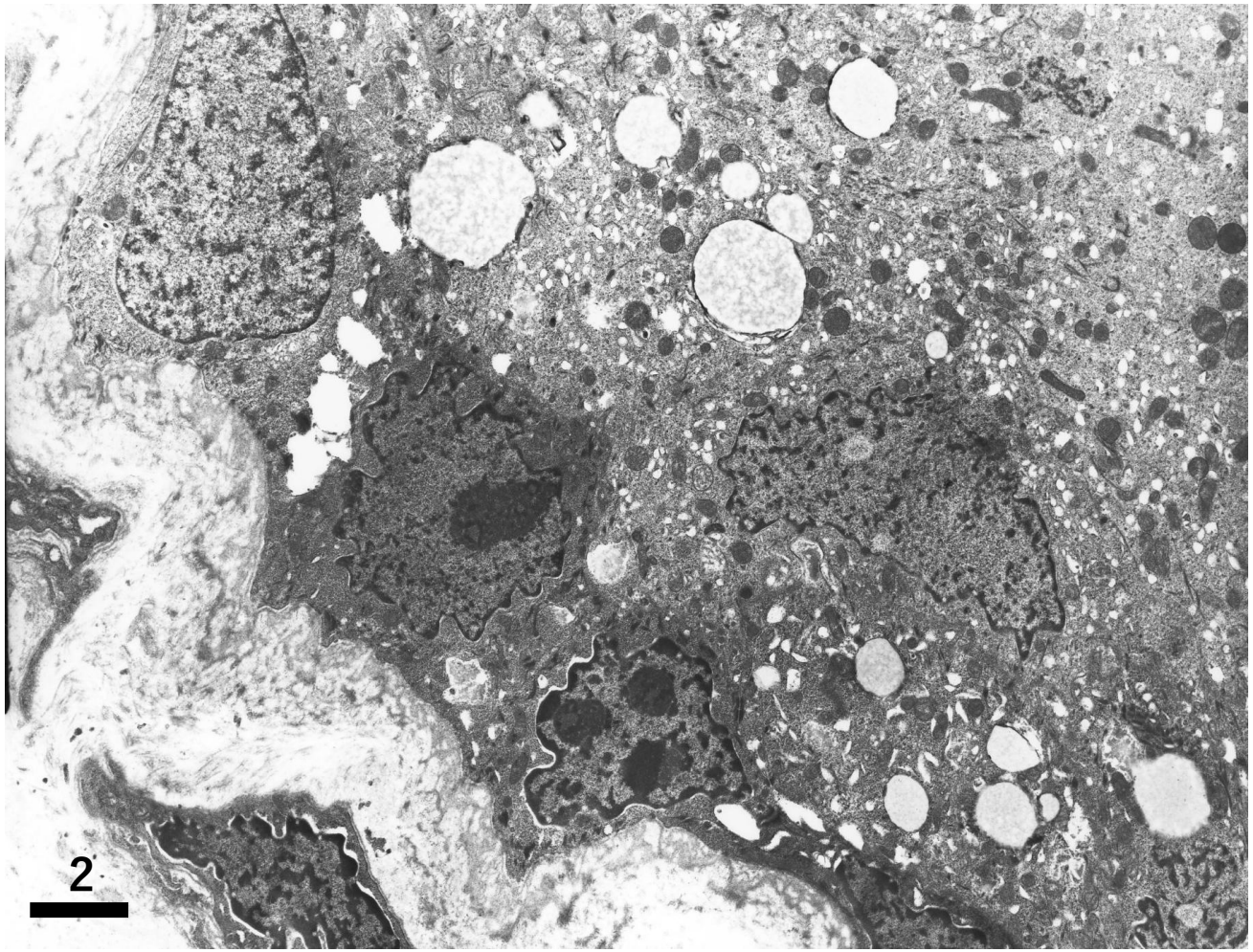
Skin biopsy from a 16-year-old boy (onset at 13 years old) shows unremarkable histology. Close examination reveals a few intracytoplasmic small PAS-positive inclusion bodies in myoepithelial cells of the eccrine sweat gland ducts. PAS-1



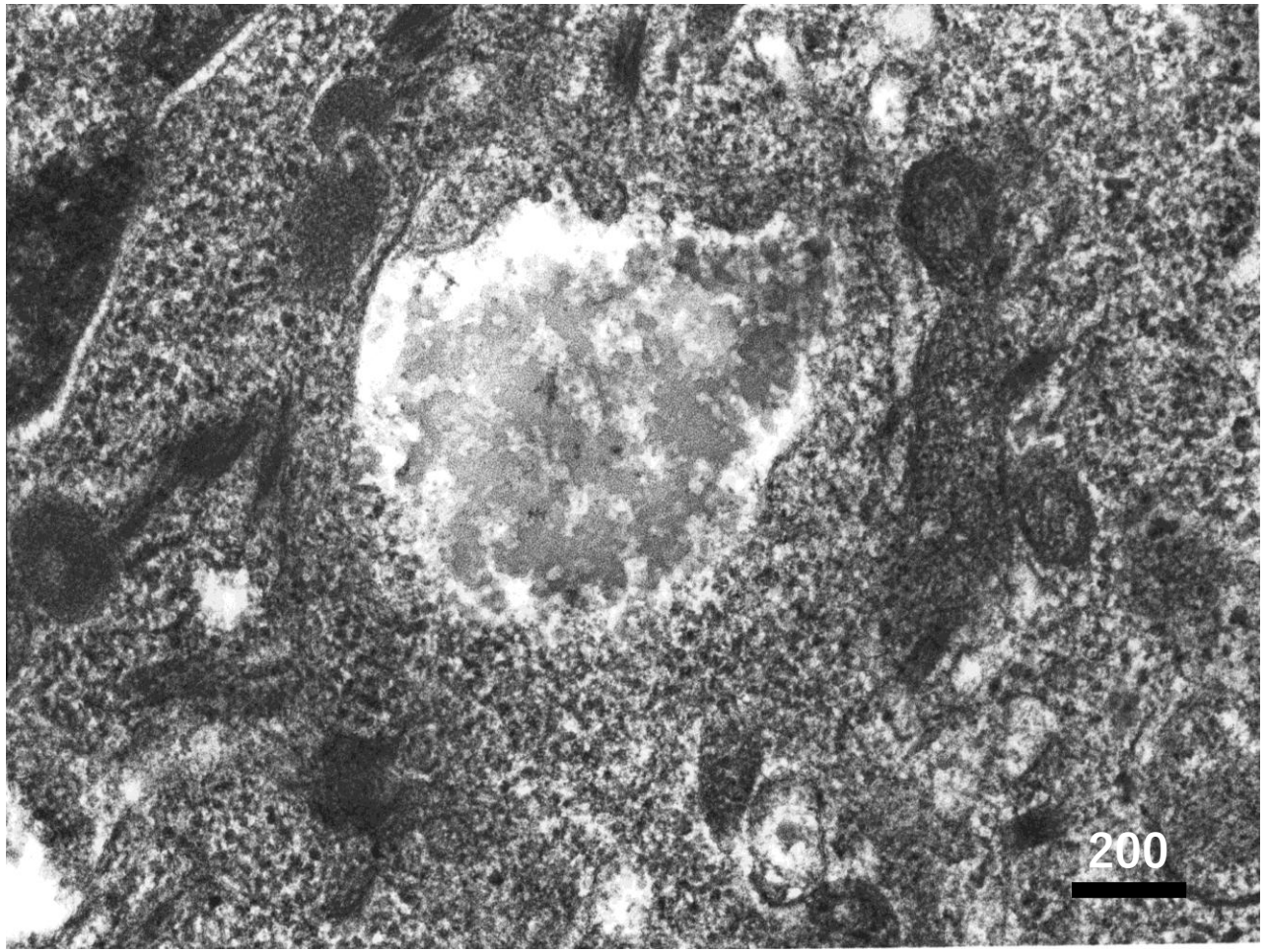
Skin biopsy from a 16-year-old boy (onset at 13 years old) shows unremarkable histology. The eccrine sweat gland ducts are shown. No inclusion bodies are recognizable. H&E-2



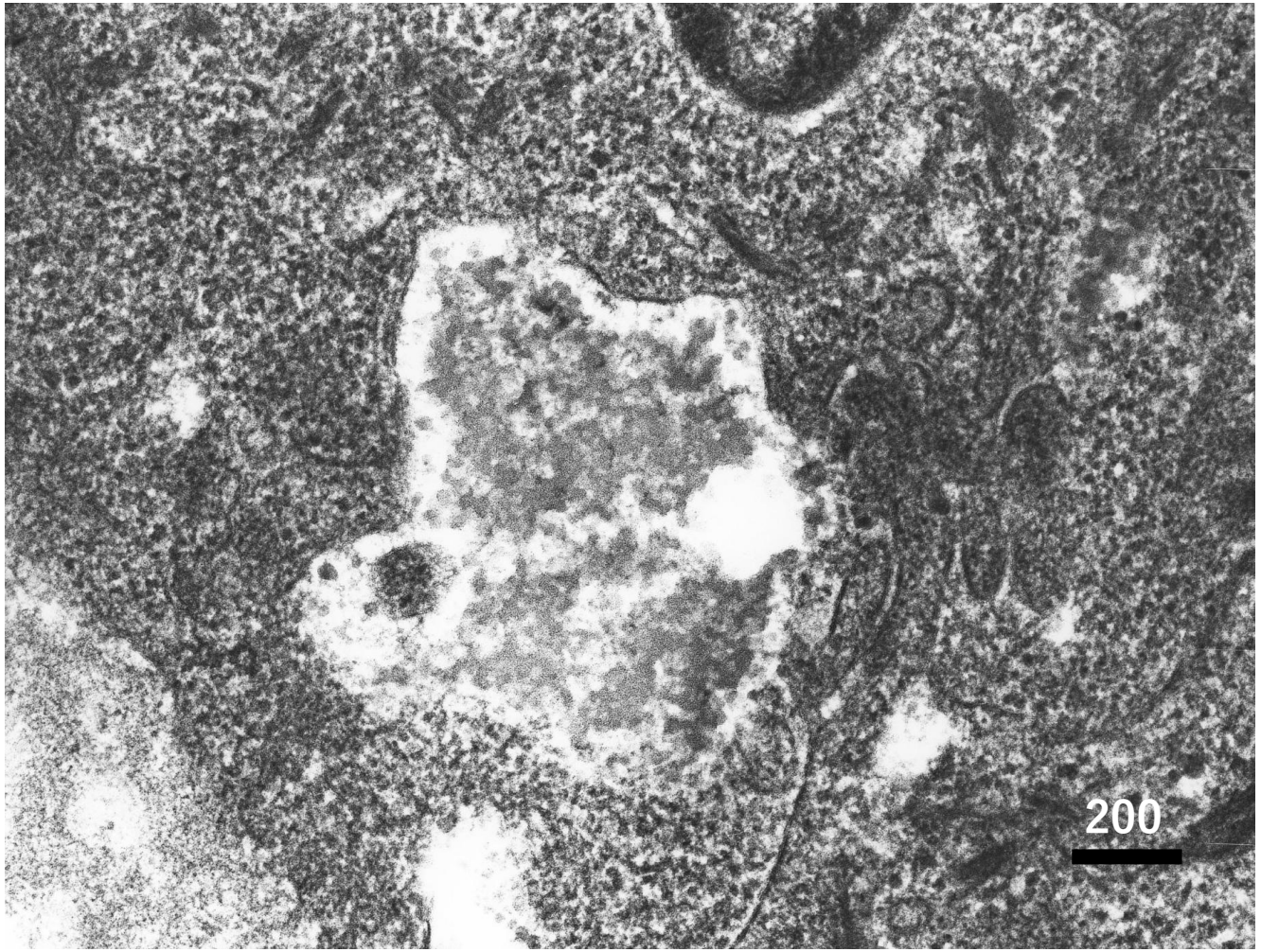
Skin biopsy from a 16-year-old boy (onset at 13 years old) shows unremarkable histology. Close examination reveals a few intracytoplasmic small PAS-positive inclusion bodies in myoepithelial cells of the eccrine sweat gland ducts. PAS-2



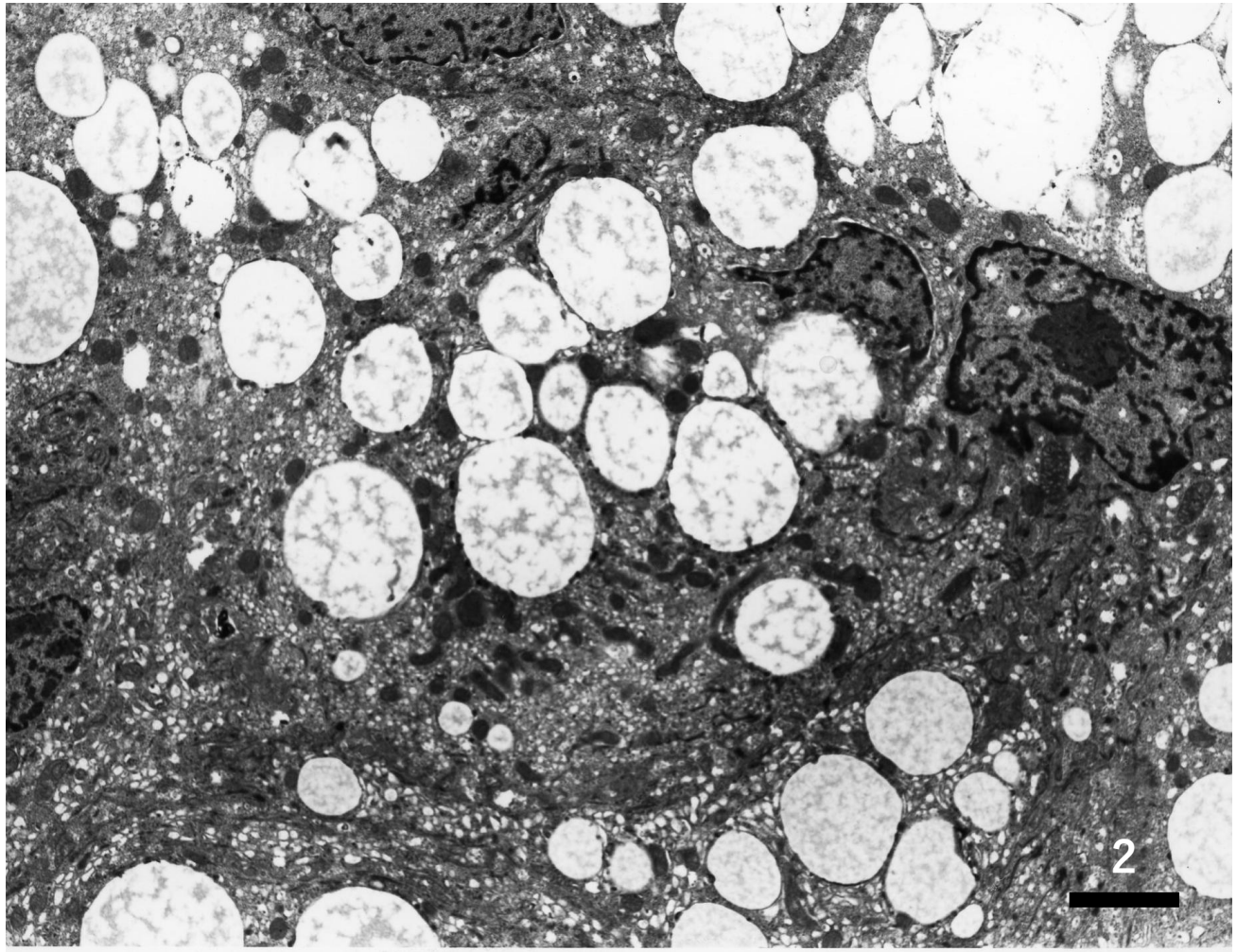
Electron microscopic study of the skin biopsy specimen reveals small (1-3 μm-sized) intracytoplasmic vacuoles in the myoepithelial cells of the eccrine sweat gland. EM-1



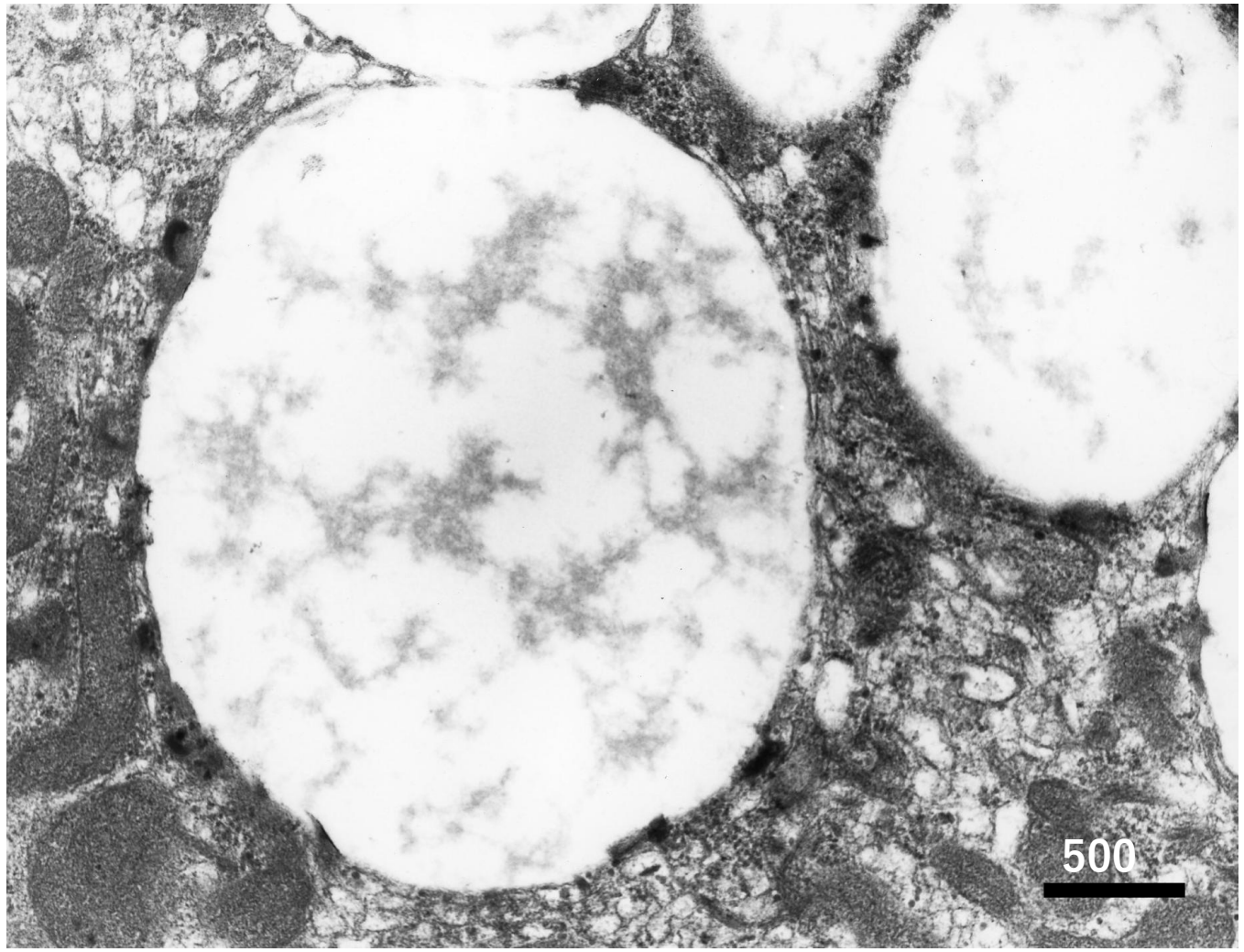
Electron microscopic study of the skin biopsy specimen reveals intracytoplasmic vacuoles in the myoepithelial cells of the eccrine sweat gland. In the vacuole, amorphous or filamentous materials with light electron density are intermingled with electron-dense aggregations. EM-2



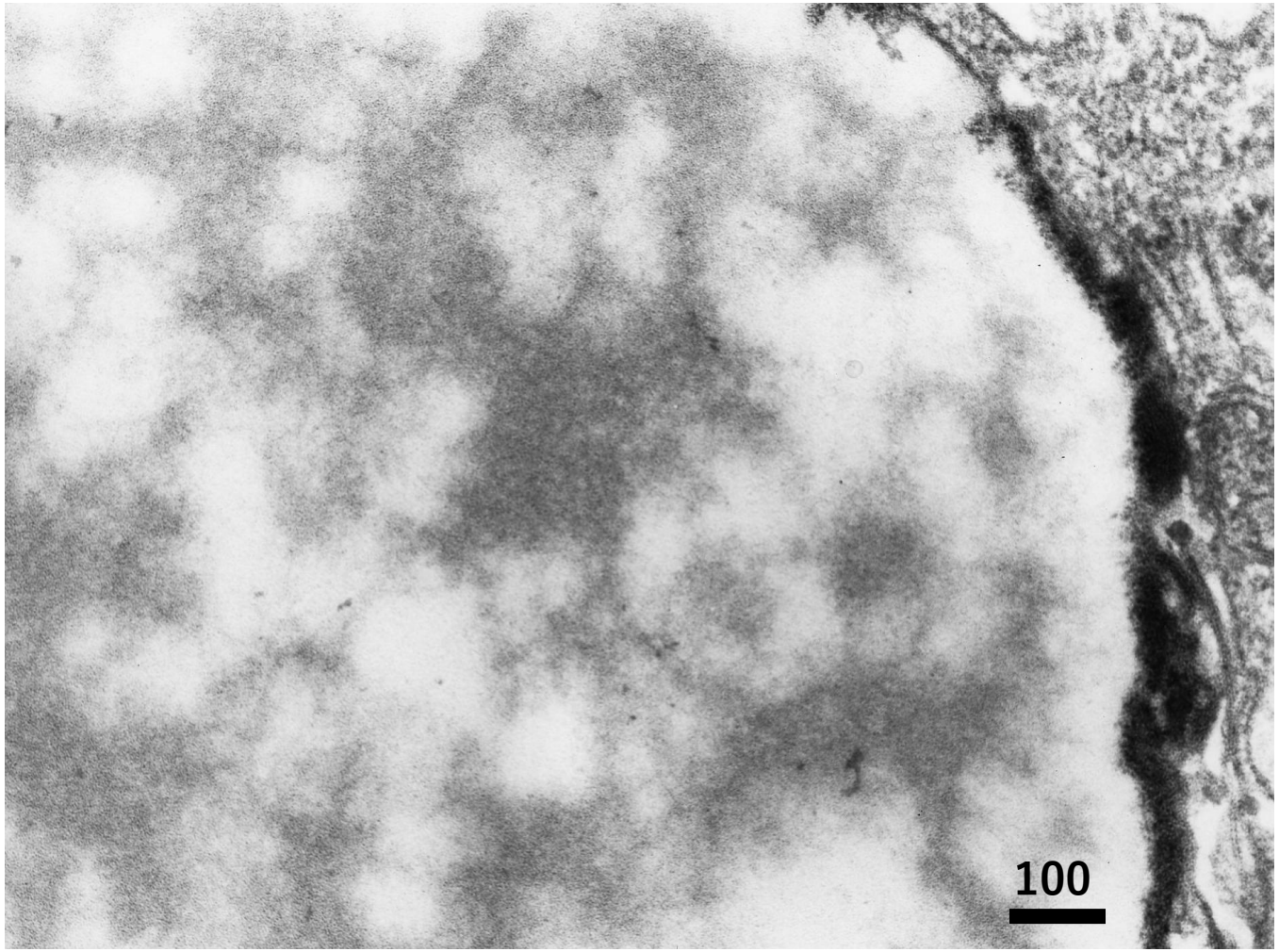
Electron microscopic study of the skin biopsy specimen reveals intracytoplasmic vacuoles in the myoepithelial cells of the eccrine sweat gland. In the vacuole, amorphous or filamentous materials with light electron density are intermingled with electron-dense aggregations. EM-3



Electron microscopic study of the skin biopsy specimen reveals small (1-4 μm-sized) intracytoplasmic vacuoles in the myoepithelial cells of the eccrine sweat gland. EM-4



Electron microscopic study of the skin biopsy specimen reveals intracytoplasmic vacuoles in the myoepithelial cells of the eccrine sweat gland. In the vacuole, amorphous or filamentous materials with light electron density are observed. EM-5



Electron microscopic study of the skin biopsy specimen reveals intracytoplasmic vacuoles in the myoepithelial cells of the eccrine sweat gland. In the vacuole, amorphous or filamentous materials with light electron density are observed. EM-6