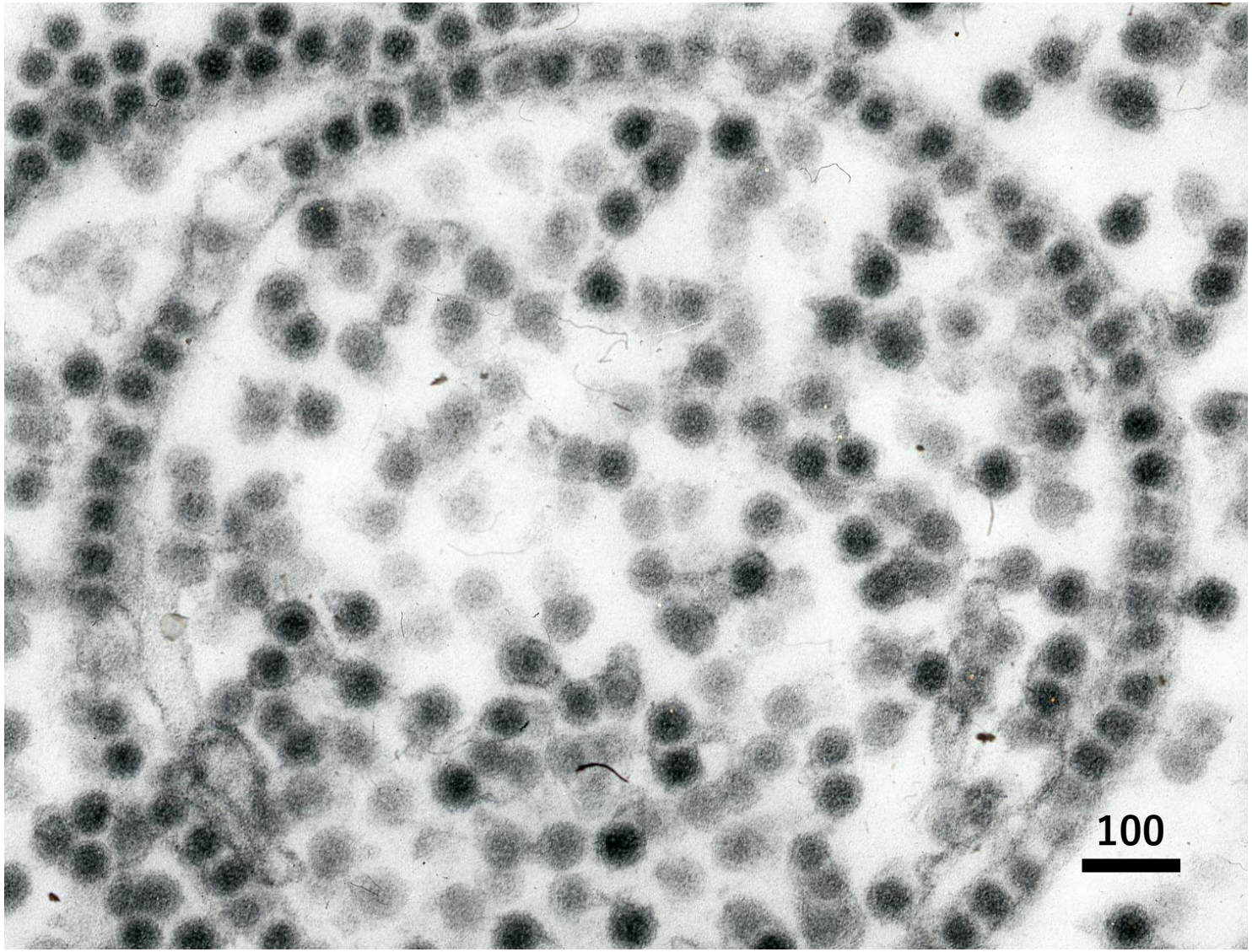
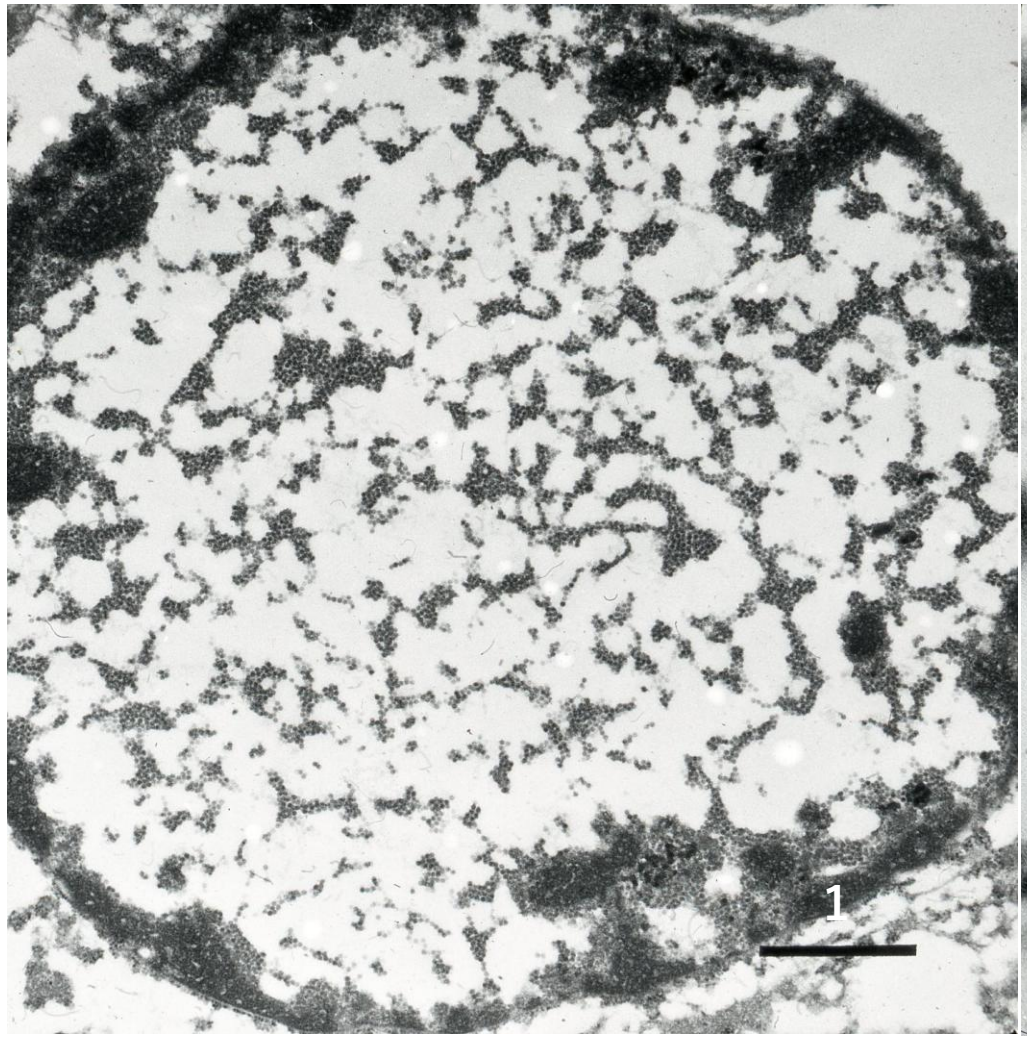
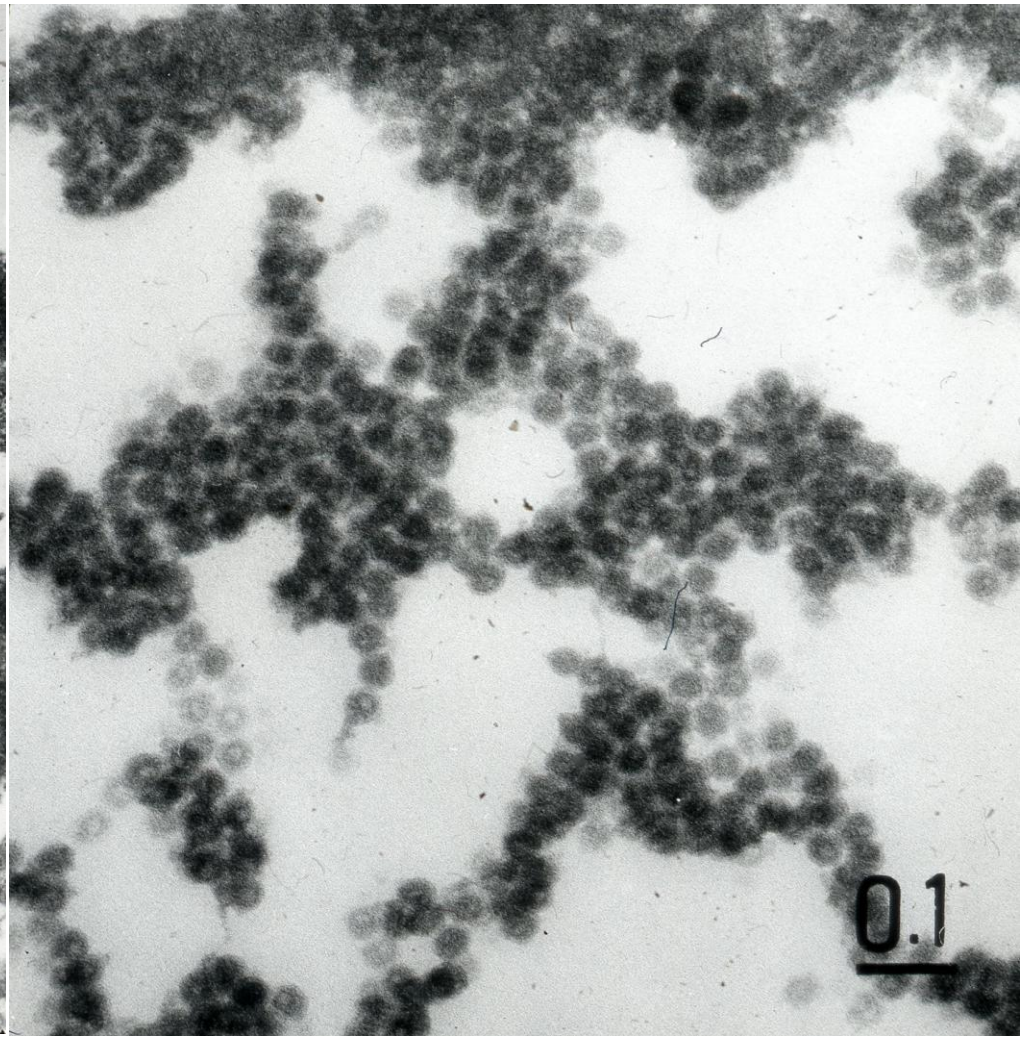
Ultrastructure of viruses

A variety of electron microscopic features of viral infections are shown here. In addition to conventional transmission electron microscopy (TEM) and scanning electron microscopy (SEM), immunostaining and *in situ* hybridization for pathogens at the ultrastructural level are presented. Please enjoy the variety.

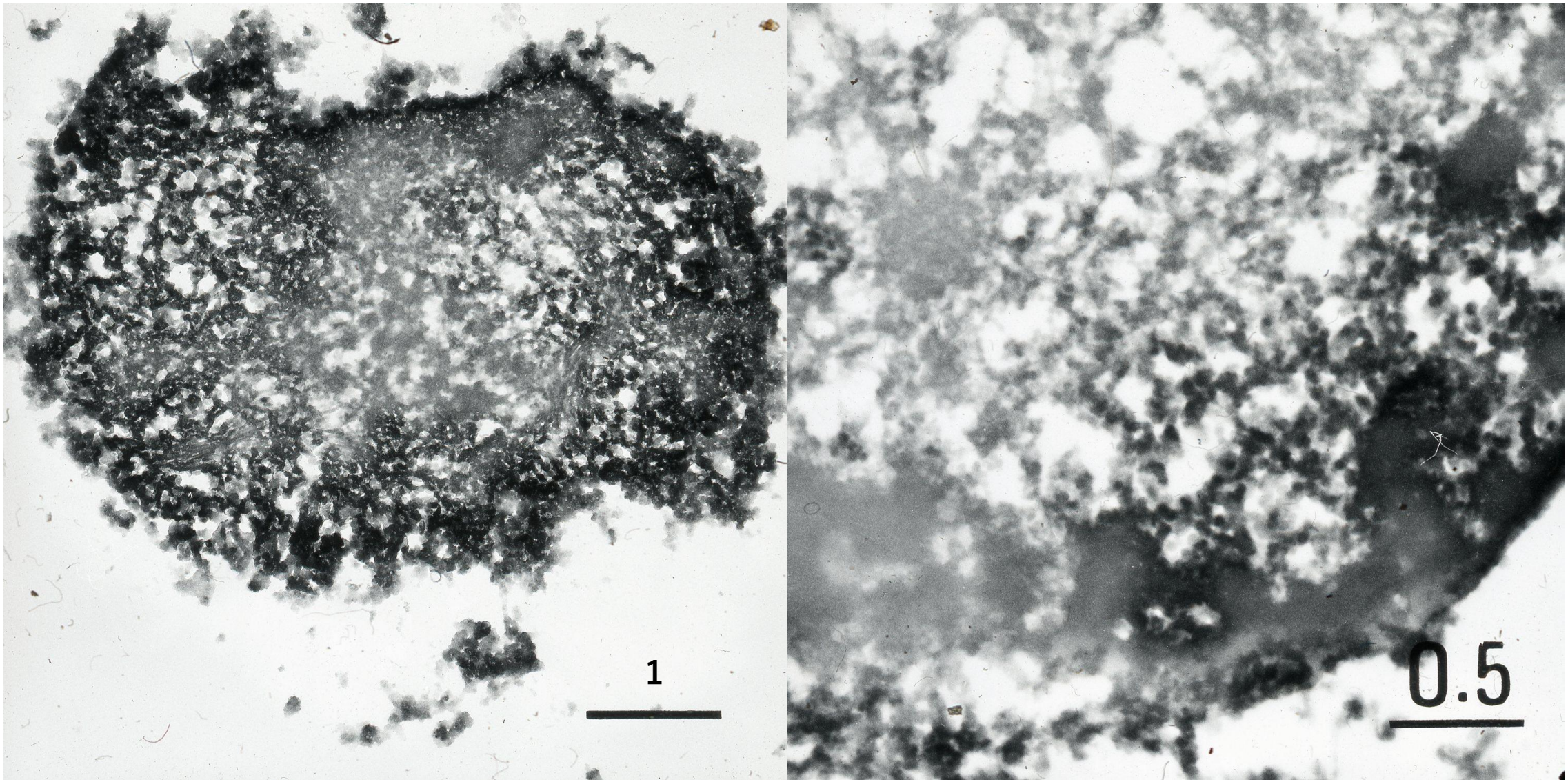


BK virus in the nucleus of the urothelial cell (decoy cell) of a 49 y-o female patient with SLE under prolonged steroid treatment. Ultrastructural study of the urine sediment (TEM). Small-sized viral particles are clustered in the nucleus.

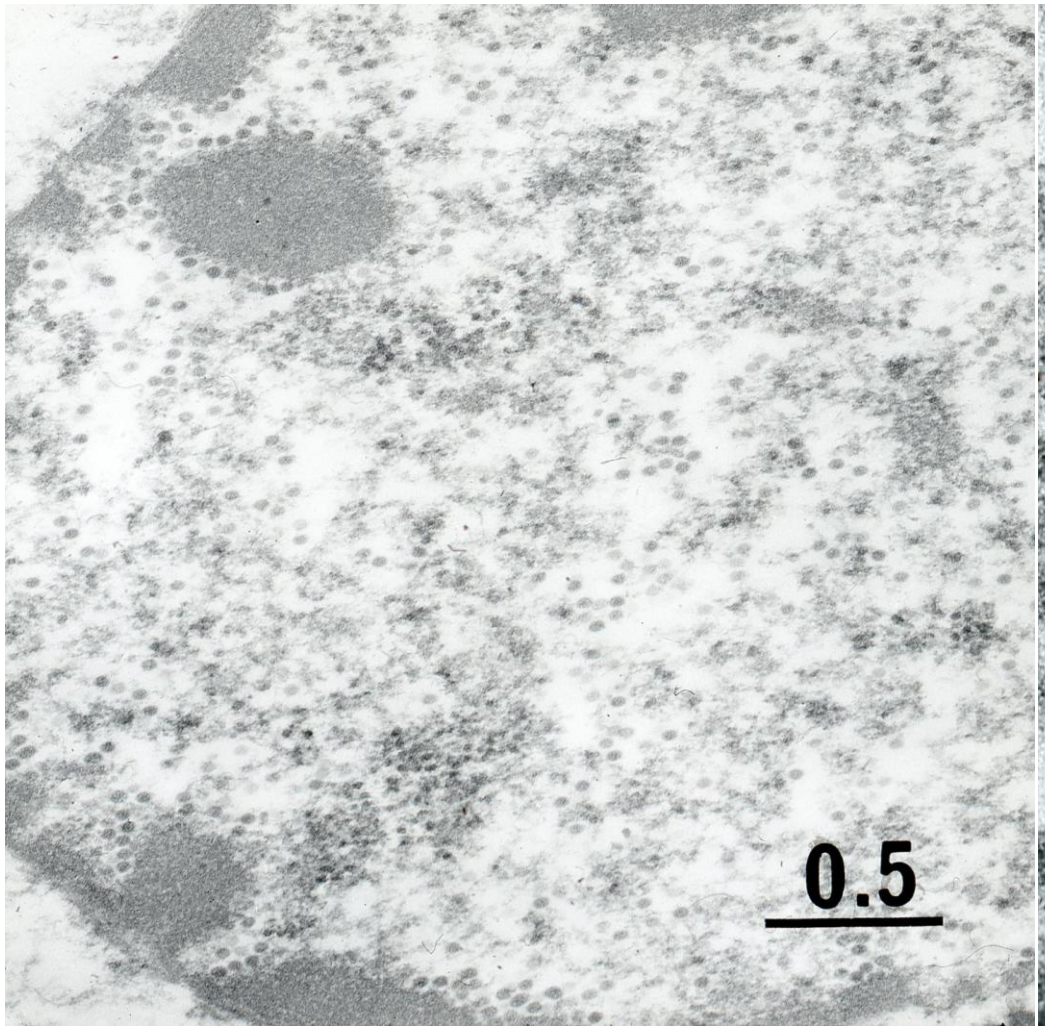


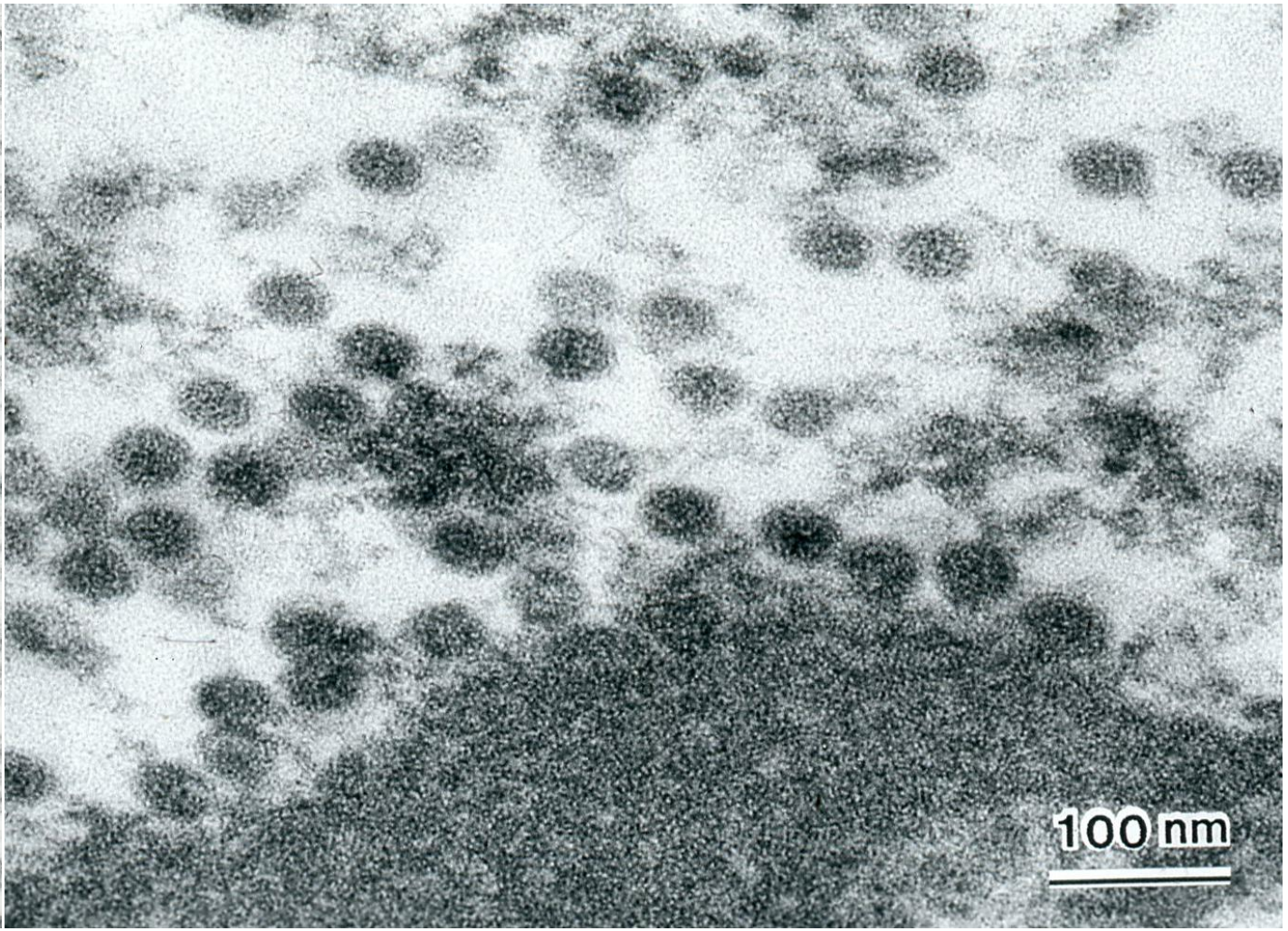


BK virus infection of the urinary bladder mucosa of a 10 y-o boy after bone marrow transplantation for ALL. At autopsy, the surface urothelial cells show intranuclear inclusion bodies. The infected cells in formalin-fixed, paraffin-embedded sections were targeted for EM study. Small-sized viral particles are irregularly clustered in the nucleus.

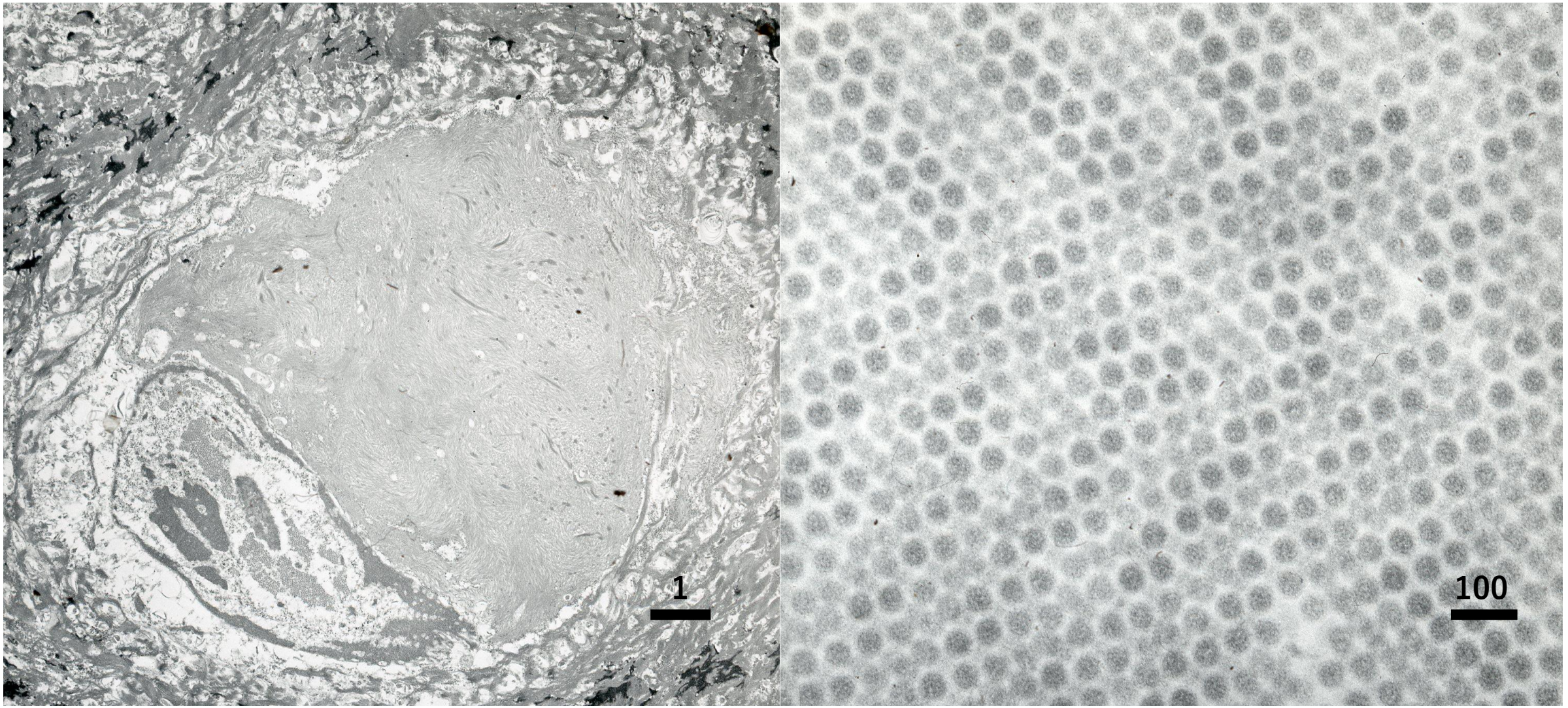


JC virus infection in progressive multifocal encephalopathy (PML) seen in an SLE patient under prolonged steroid treatment. The nucleus of an oligodendroglia is filled with JC virus antigen-positive viral particles. Pre-embedding immunoelectron microscopy using formalin-fixed, paraffin-embedded sections.

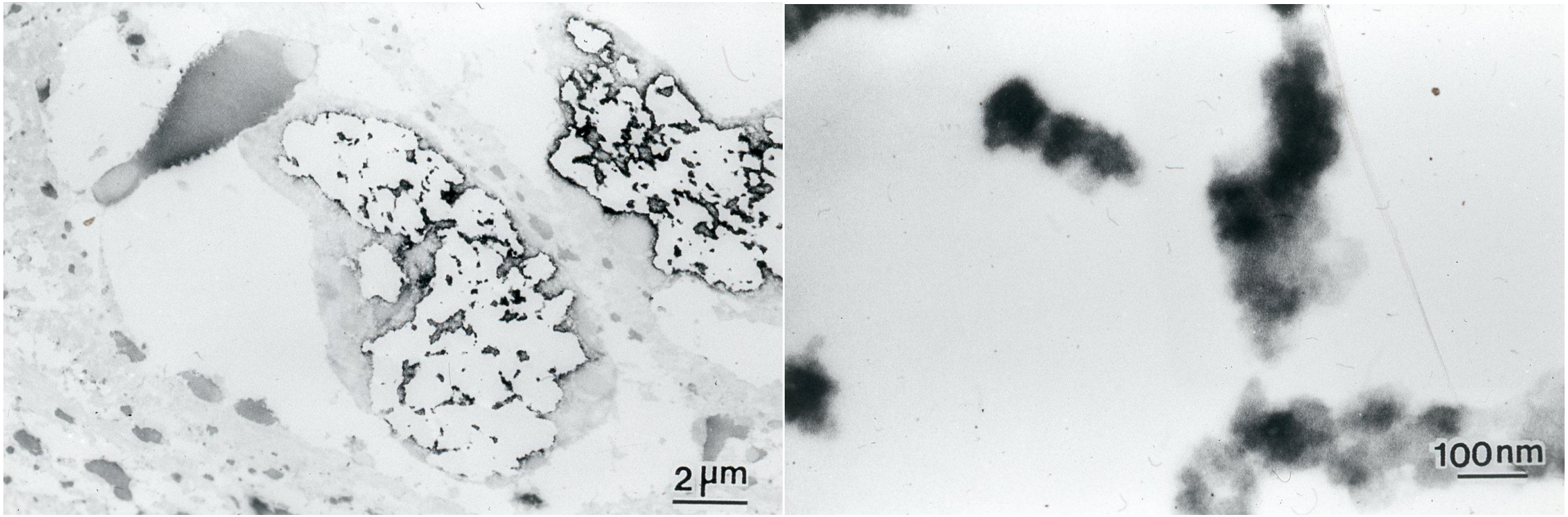




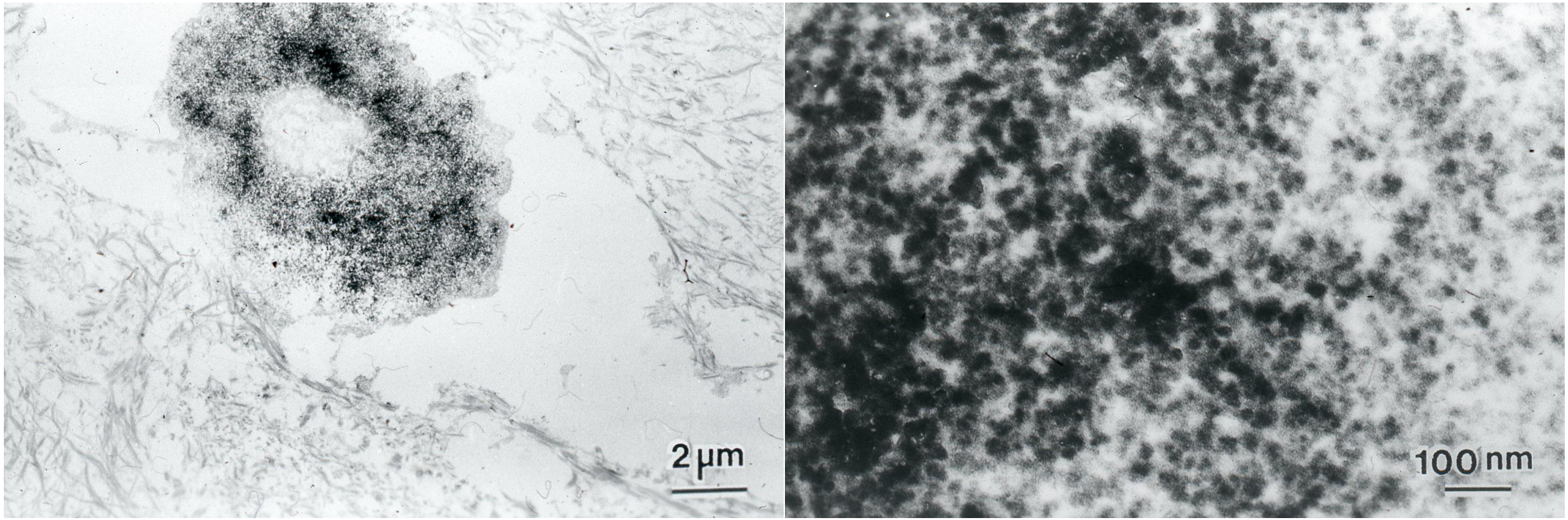
Verruca vulgaris of the child foot skin (TEM). The nucleus of the koilocyte with an intranuclear viral inclusion in the granular layer of the epidermis contains small-sized viral particles of papilloma-polyoma group.



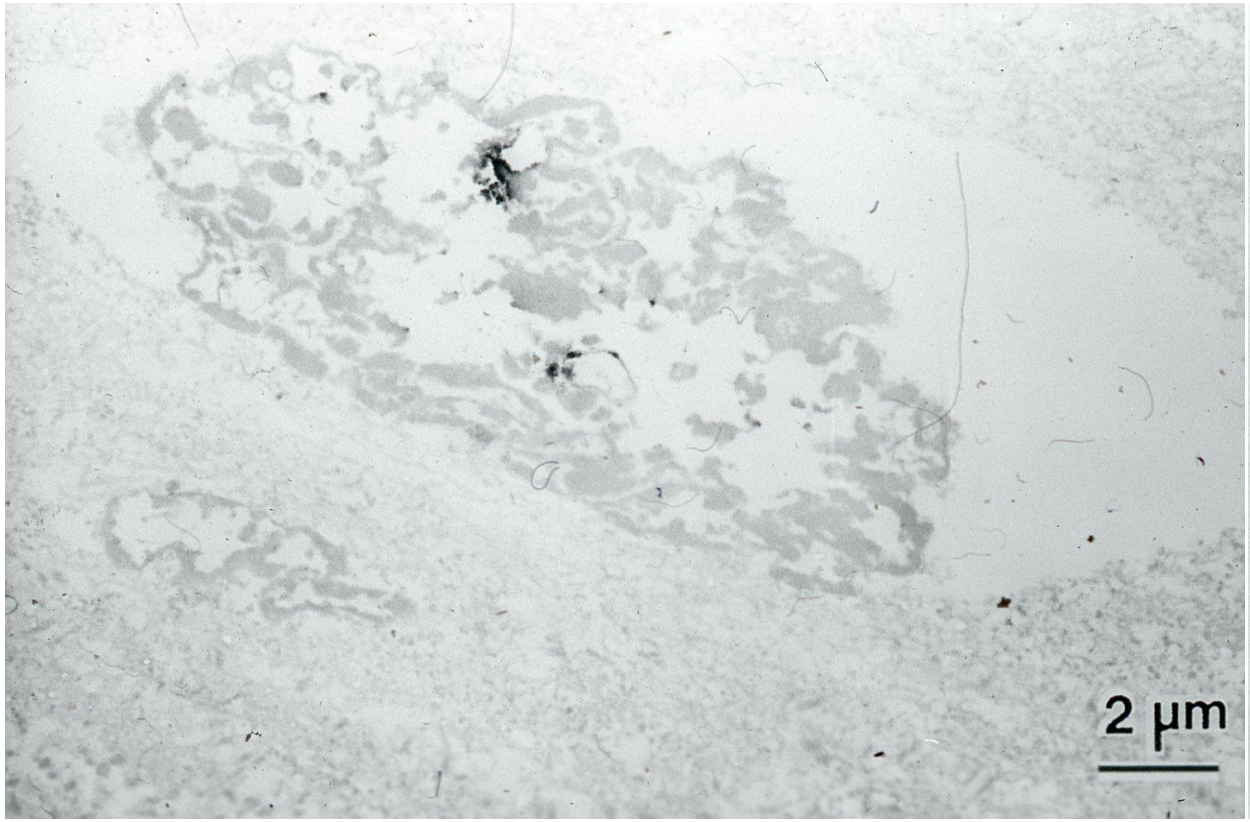
Plantar cystic wart caused by HPV-60 infection (TEM). The cytoplasm of the HPV-infected cell contain a large intracytoplasmic hyaline globule (viral infection-related but without viral particles). The small-sized viral particles are densely located within the nucleus.

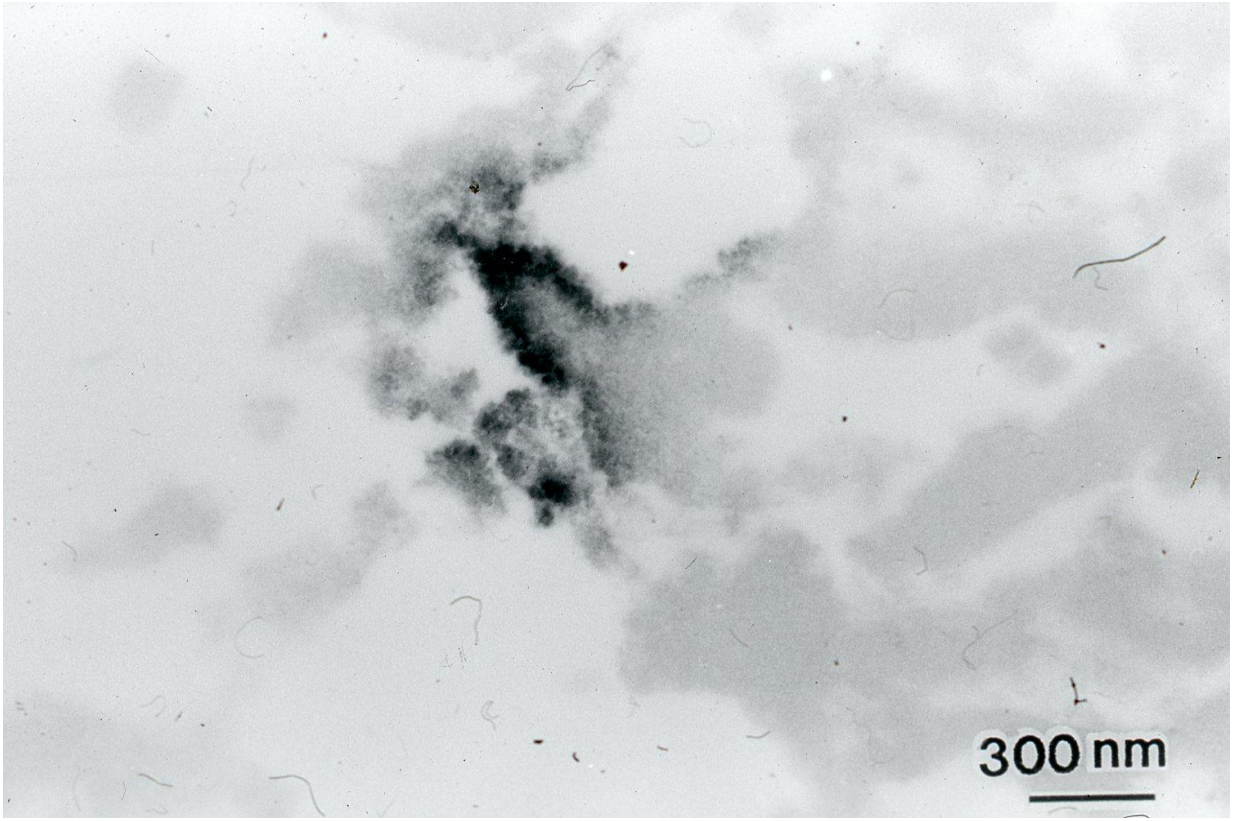


Verruca vulgaris. Pre-embedding immunoelectron microscopy with bovine papilloma virus antiserum. Formalin-fixed, paraffin-embedded sections were evaluated. Keratohyaline granules are seen in the cytoplasm of the haloed keratinocyte. Small-sized (around 70 nm) intranuclear viral particles are immunolabeled. **Ref**.: Tsutsumi Y, et al. Ultrastructural visualization of human papillomavirus DNA in verrucous and precancerous squamous lesions. Acta Pathol Jpn 1991; 41(10): 757-762. doi: 10.1111/j.1440-1827.1991.tb03348.x

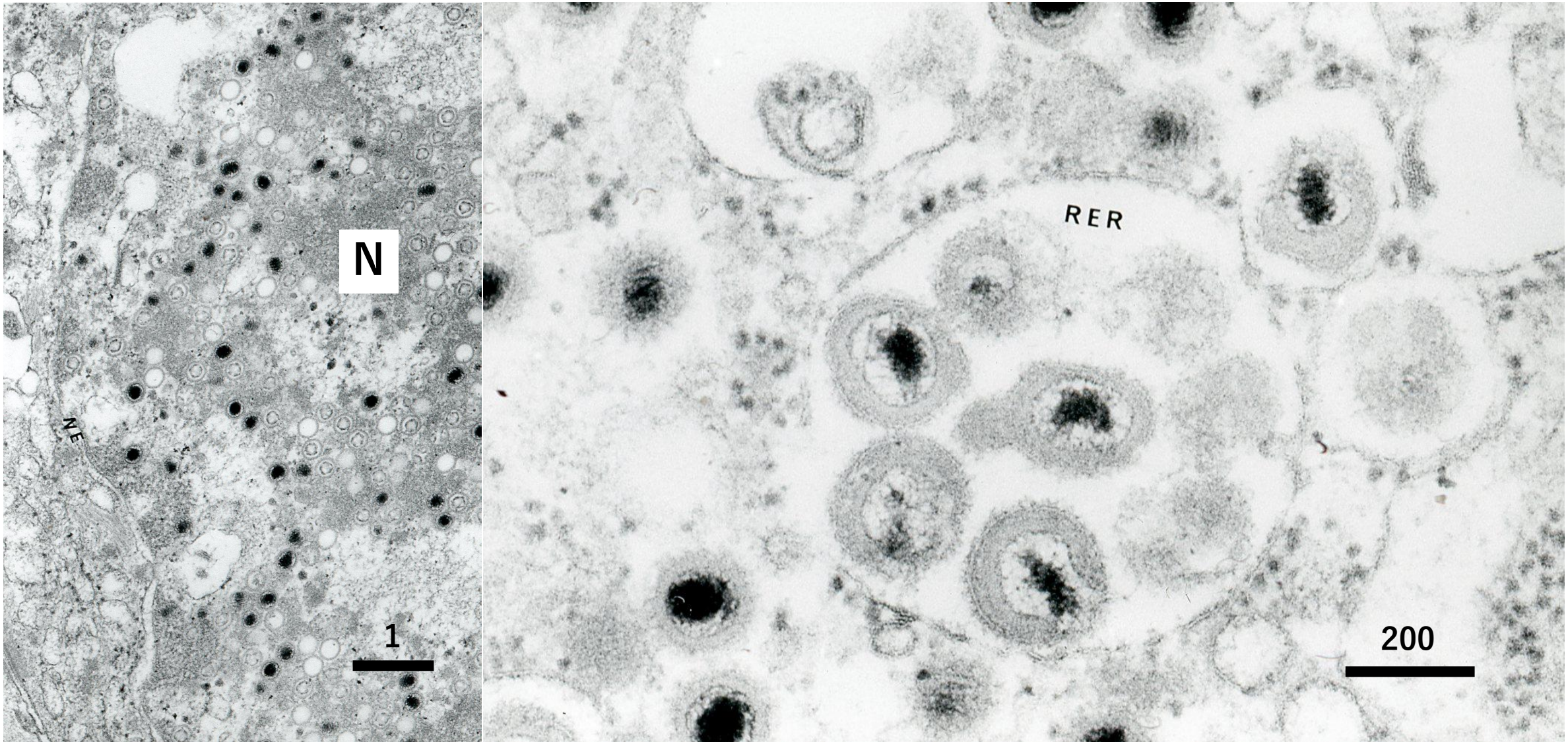


Condyloma acuminatum of the vulva. The nucleus is densely labeled with biotinylated DNA probe for HPV 6/11. The size of the positive signals (15-20 nm) is much smaller than that of the HPV viral particles (around 70 nm). In the present lesion, immunostaining for the viral capsid antigen is only focally positive. These findings indicate the presence of the naked (plasmid) viral DNA as fine particles. **Ref**.: Tsutsumi Y, et al. Ultrastructural visualization of human papillomavirus DNA in verrucous and precancerous squamous lesions. Acta Pathol Jpn 1991; 41(10): 757-762. doi: 10.1111/j.1440-1827.1991.tb03348.x

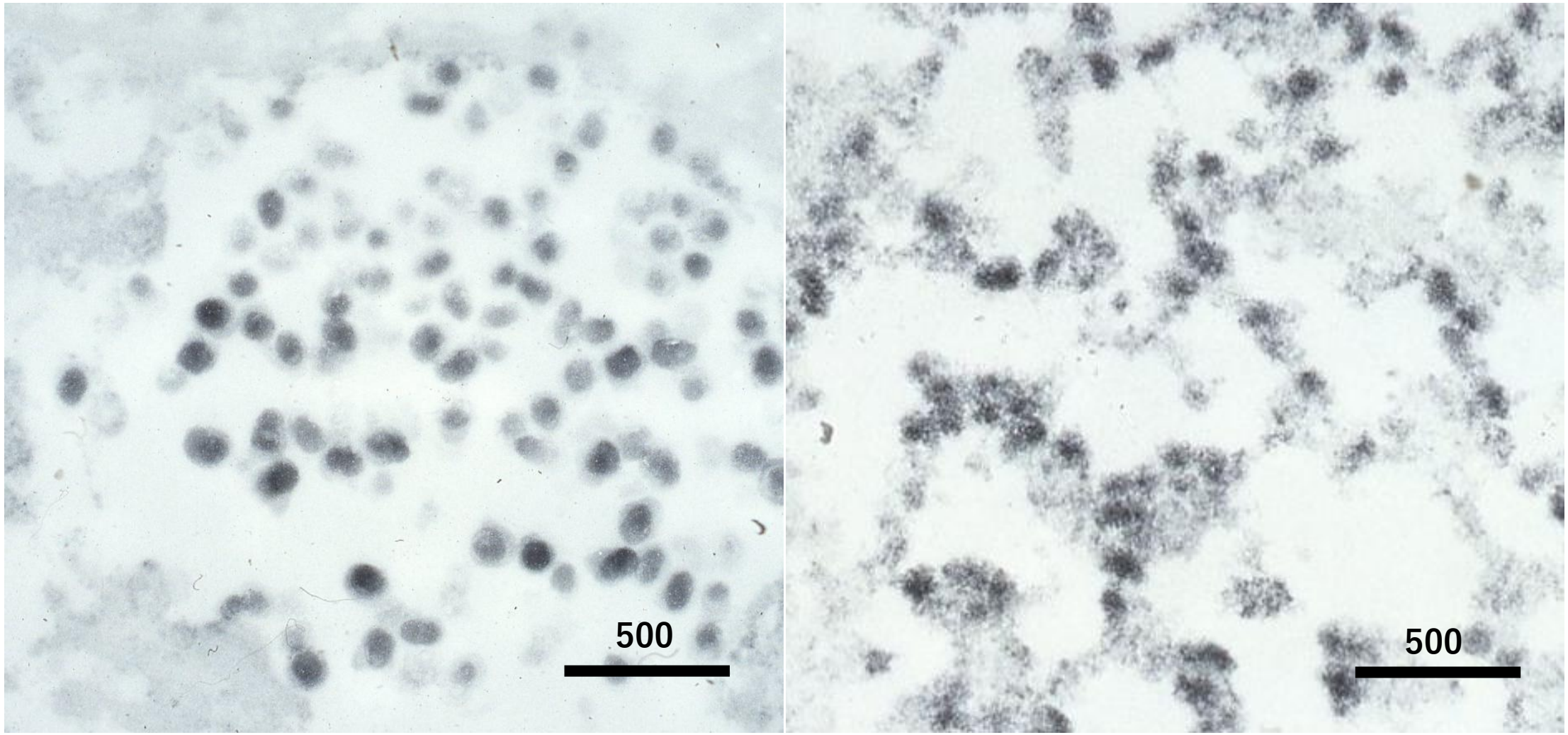




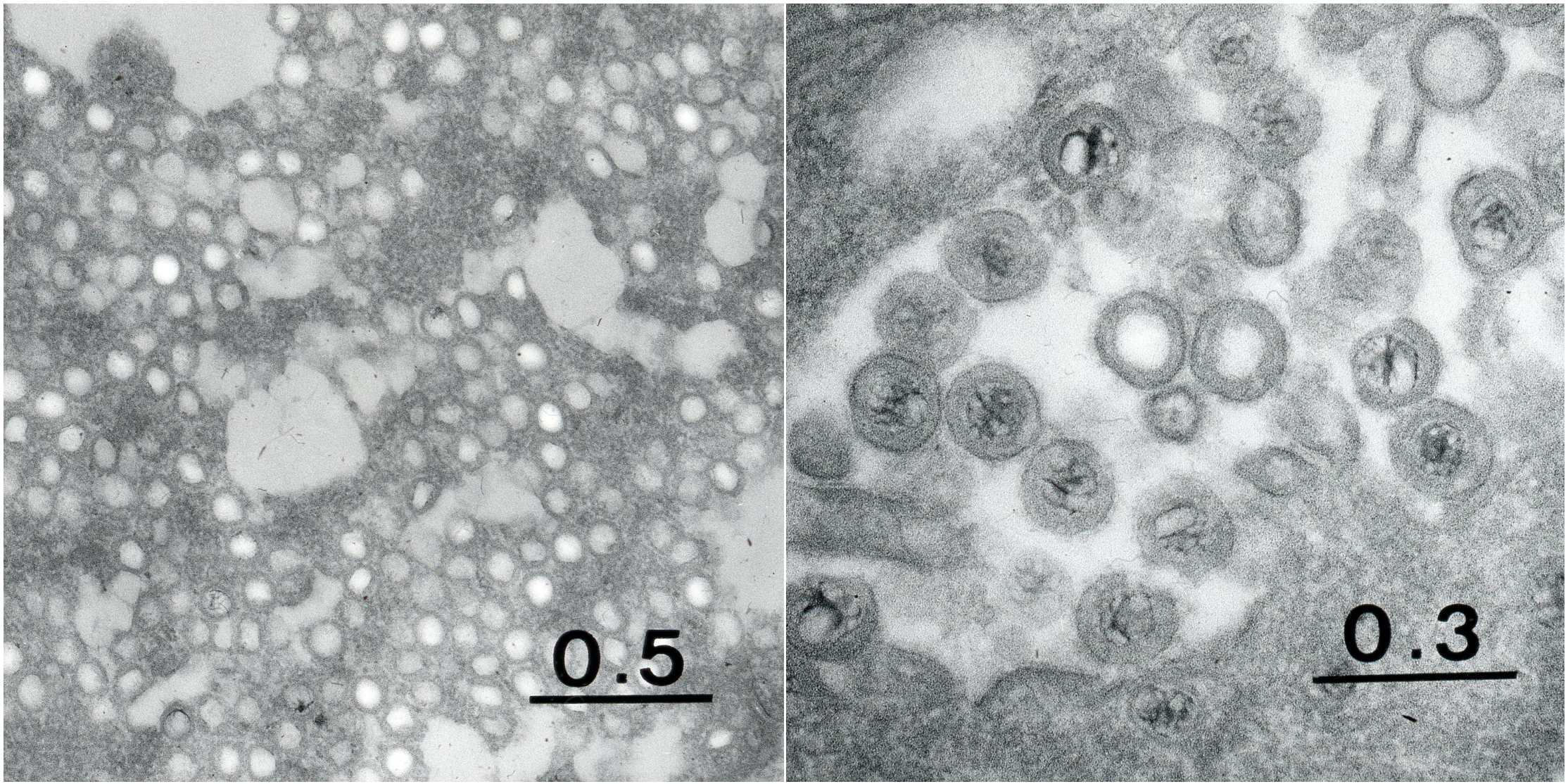
Severe dysplasia of the uterine cervix. *In situ* hybridization using a biotinylated DNA probe for HPV 16/18 demonstrates focal dot-like positivity in the nucleus of the dysplastic cell. The positive signals seem to be seen on a part of chromatin, indicating the integration of the viral DNA into the host cell DNA. **Ref**.: Tsutsumi Y, et al. Ultrastructural visualization of human papillomavirus DNA in verrucous and precancerous squamous lesions. Acta Pathol Jpn 1991; 41(10): 757-762. doi: 10.1111/j.1440-1827.1991.tb03348.x



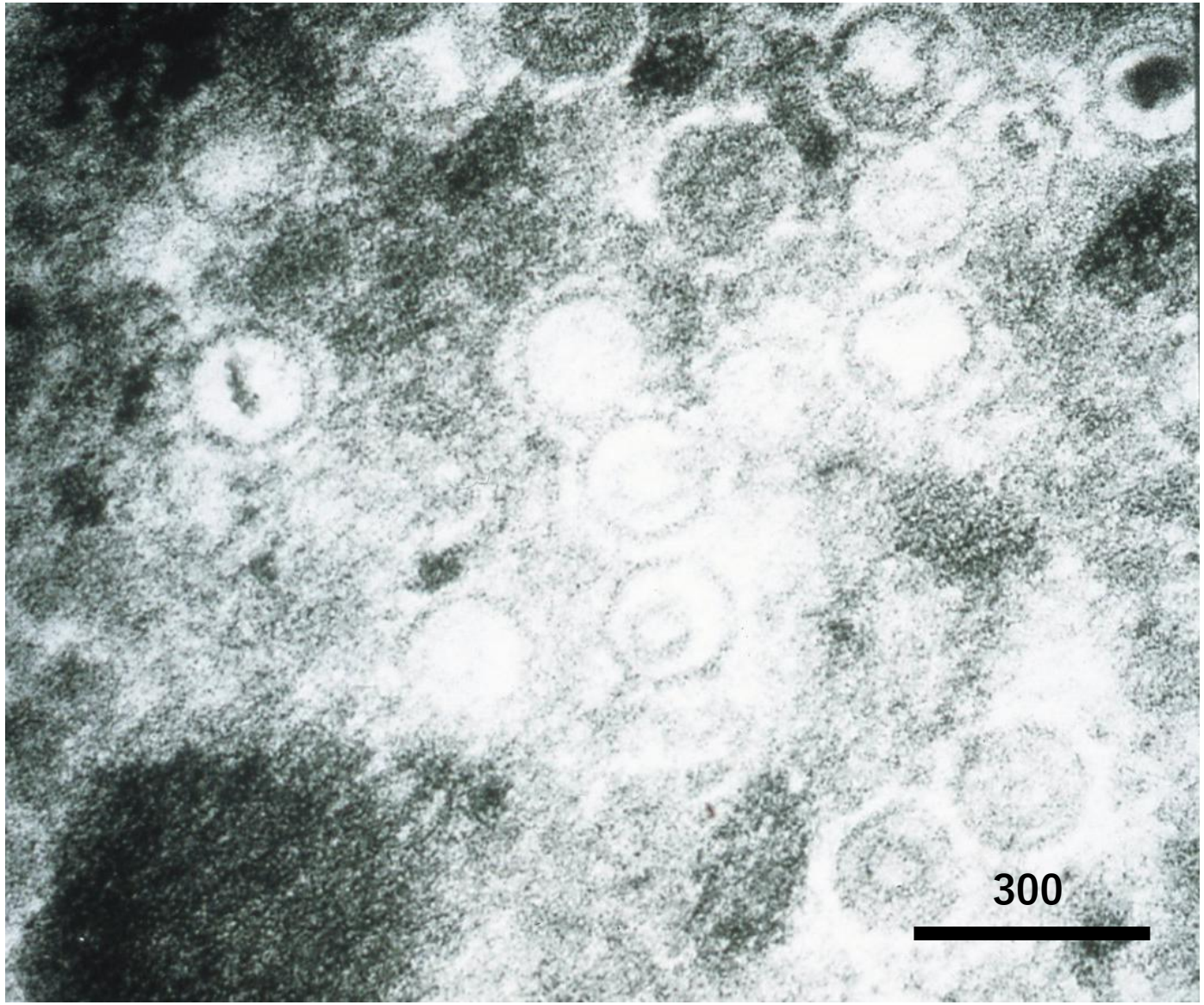
CMV infection of the lung (TEM). The pulmonary epithelial cell contains viral particles in both the nucleus (N) and cytoplasm. In the cytoplasm, enveloped mature viral particles measuring 180 nm are observed inside and outside of the rough endoplasmic reticulum (RER).



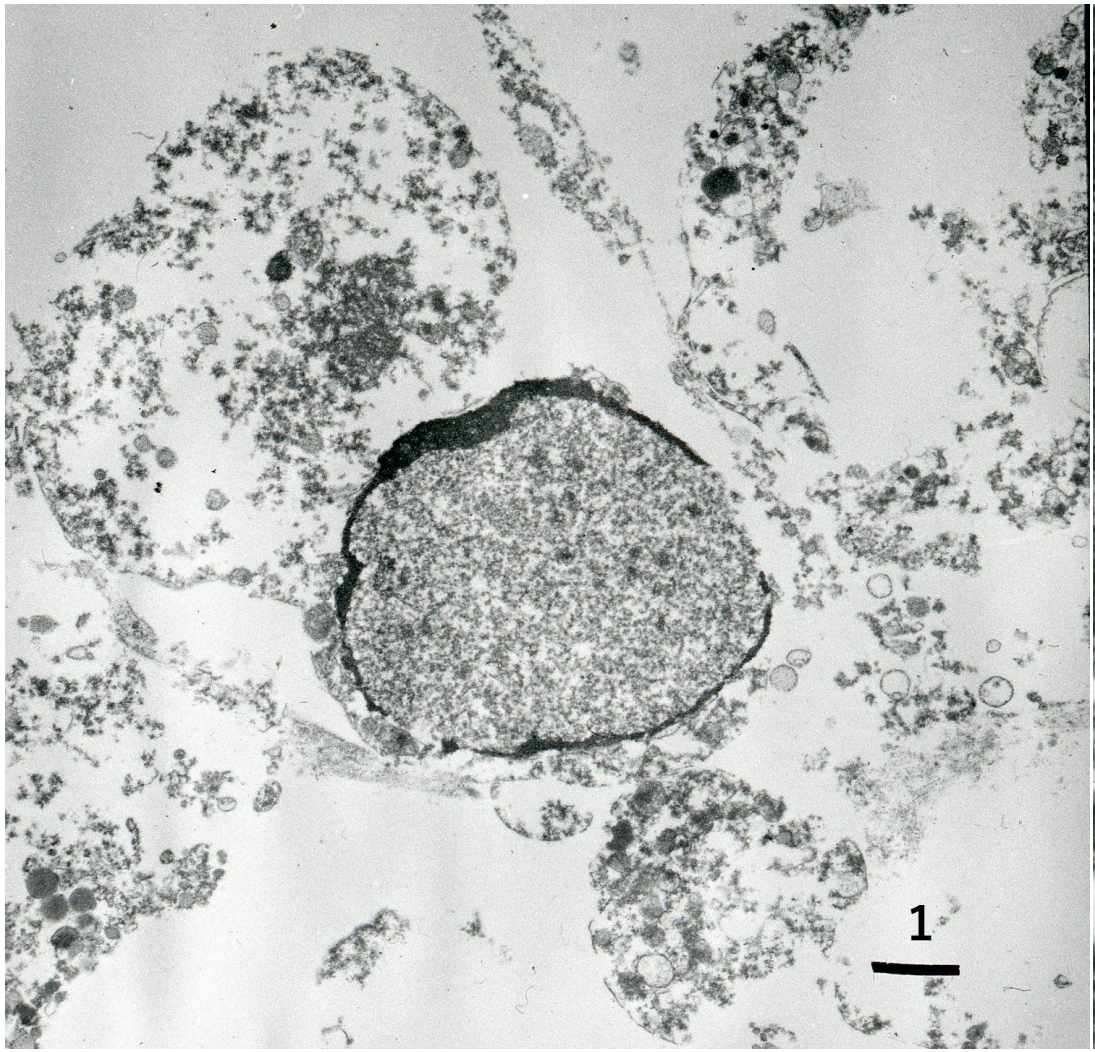
CMV infection of the lung. Specific ultrastructural detection of CMV by immunostaining (left) and *in situ* hybridization (right). The pre-embedding method using formalin-fixed, paraffin-embedded sections of the autopsy lung specifically demonstrates the viral particles in the nucleus.

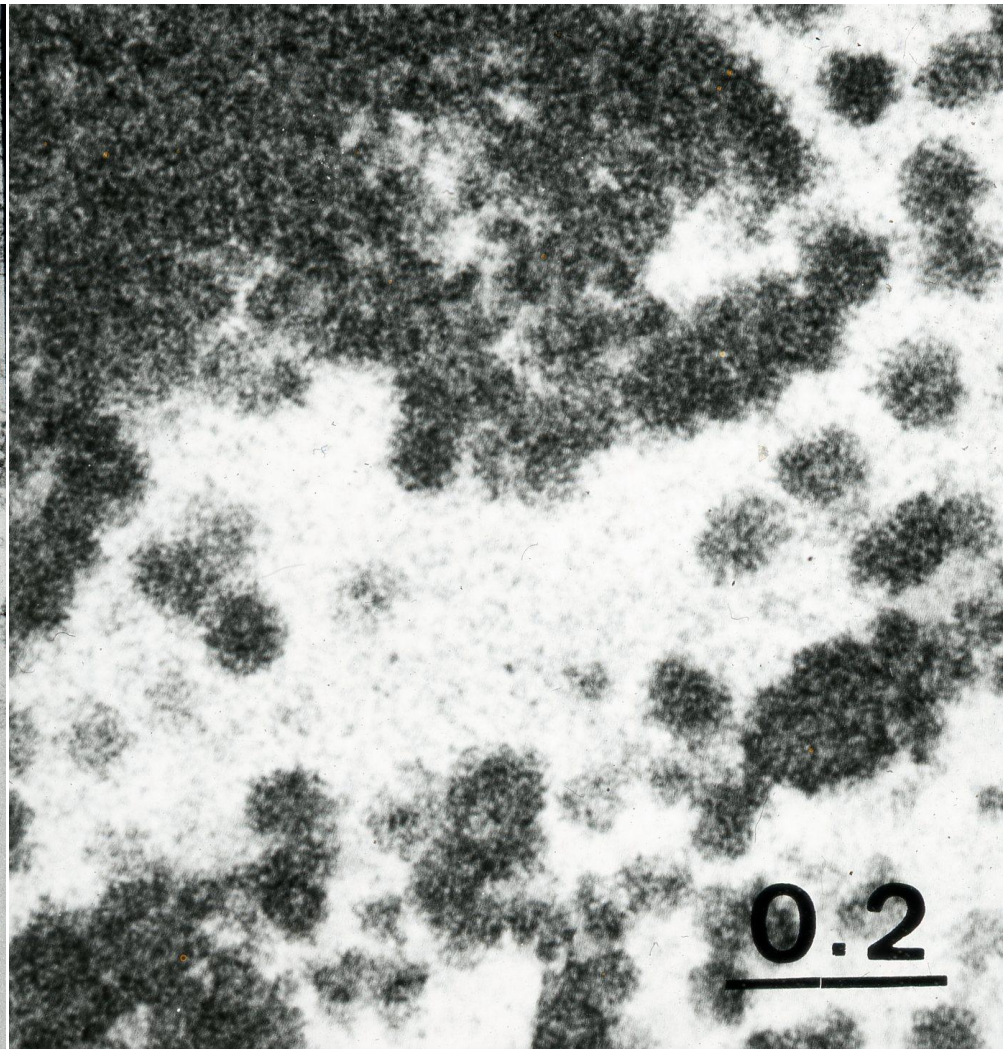


Herpes zoster of the skin (varicella-zoster virus infection) (TEM). In the nucleus, viral particles without envelop are clustered. Fine fragmented core structures can be discerned. In the cytoplasm, enveloped mature viral particles are formed in the cisterna of the rough endoplasmic reticulum. Aberrant forms without a nuclear core are often intermingled.

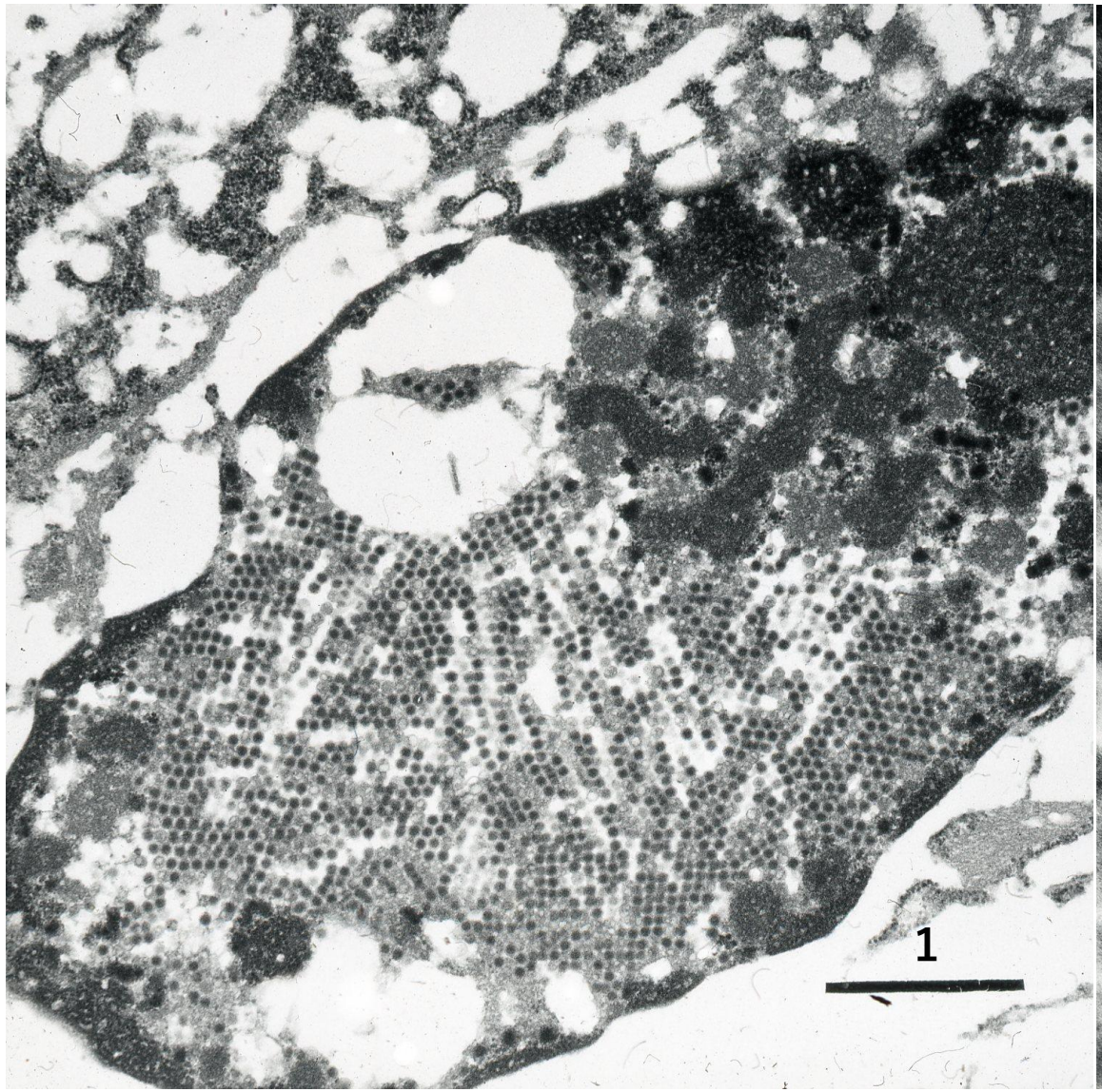


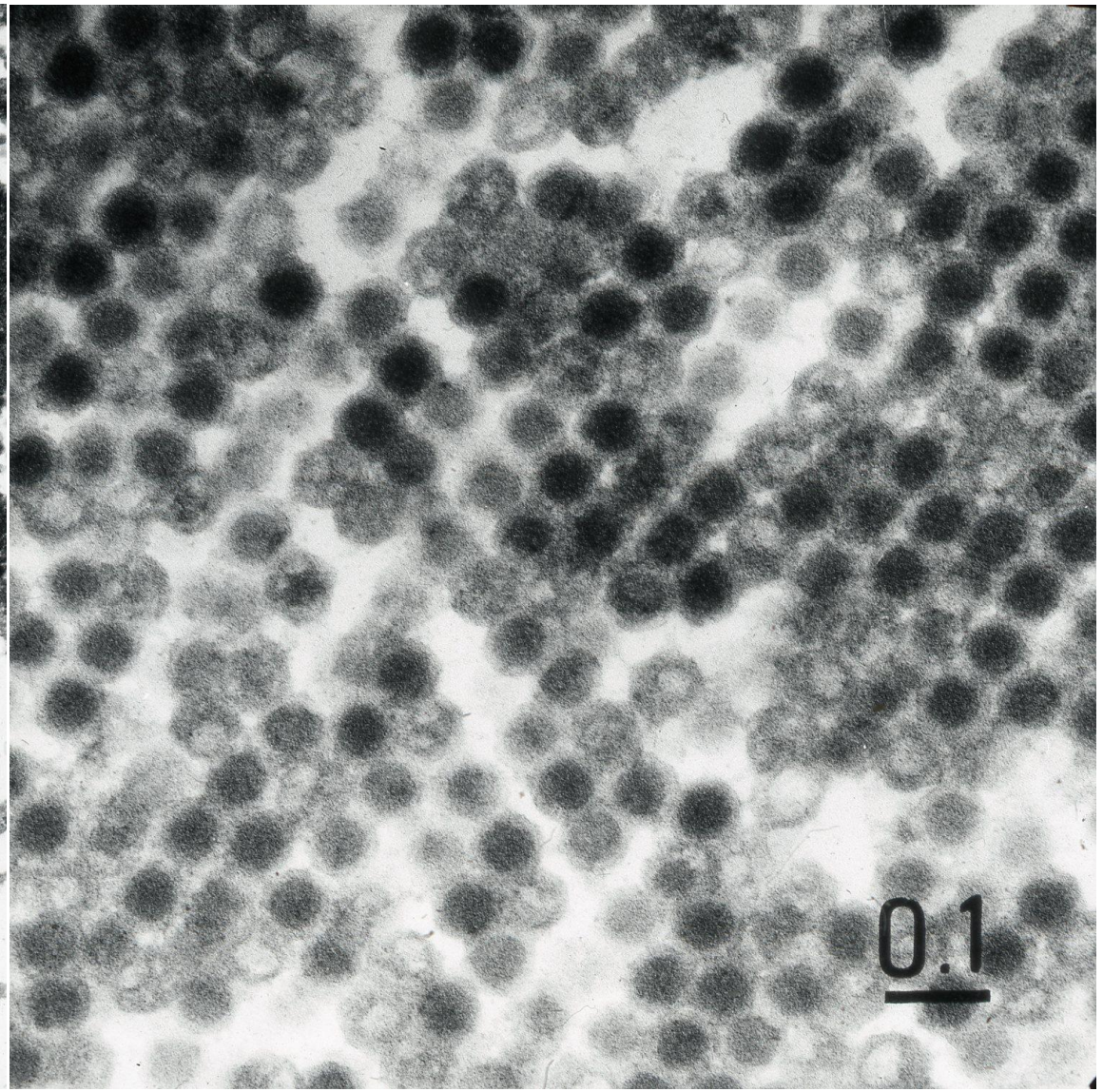
Hairy leukoplakia of the tongue (TEM). A rare type of EBV infection forming viral particles in the nucleus. The formation of intranuclear inclusions is characteristic of the diseased squamous epithelial cells.



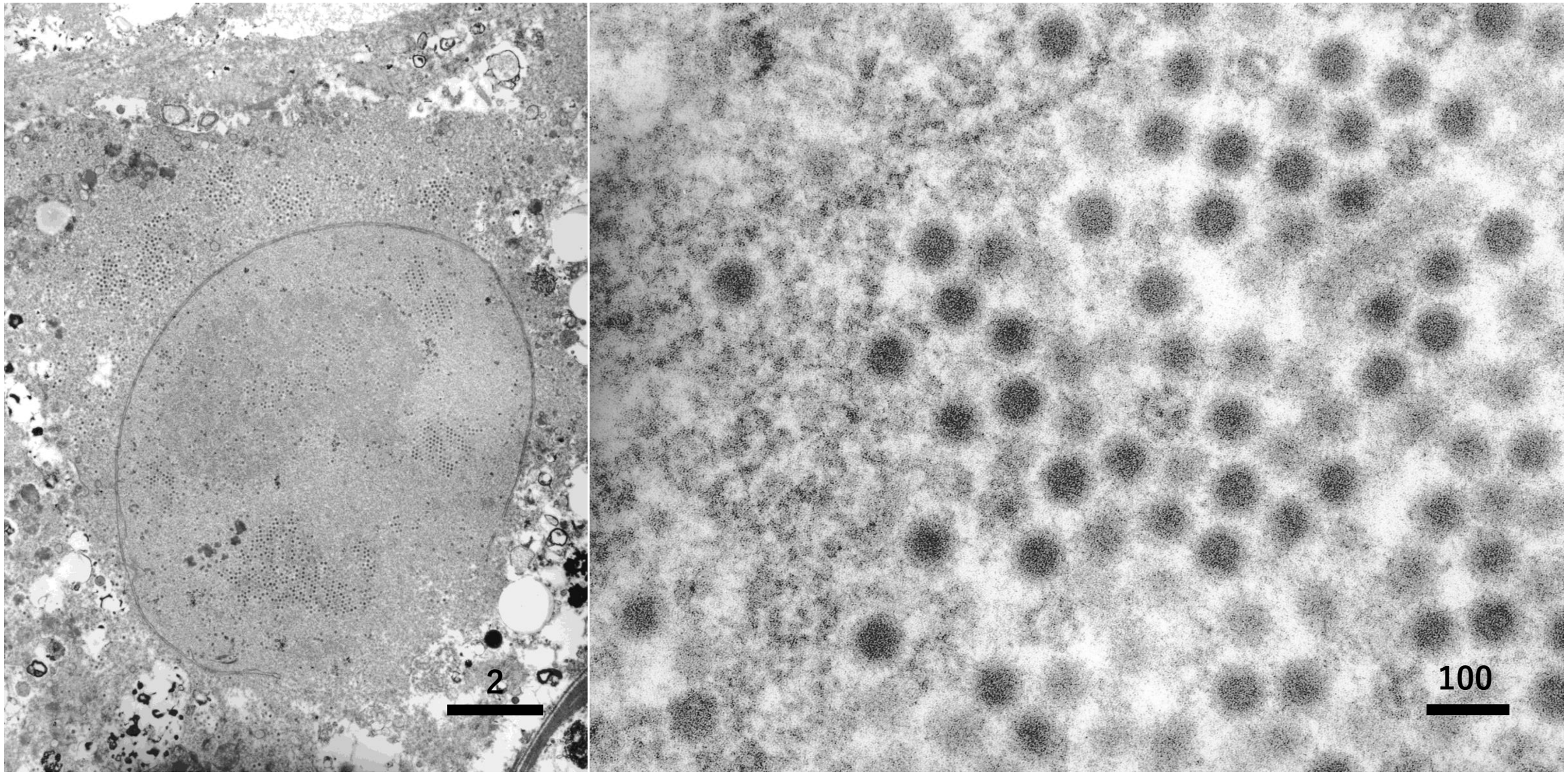


Parvovirus B19 infection complicating lethal hydrops fetalis. The mother infected erythema infectiosum at the 10th week of gestation, and the dead fetus at the 25th week of gestation accompanied severe hydrops fetalis. The nucleated erythrocyte (erythroblast) in the capillary vessel of the placenta shows intranuclear inclusion. The intranuclear unenveloped viral particles are very small (less than 20 nm in diameter) (TEM using formalin-fixed, paraffin-embedded section).

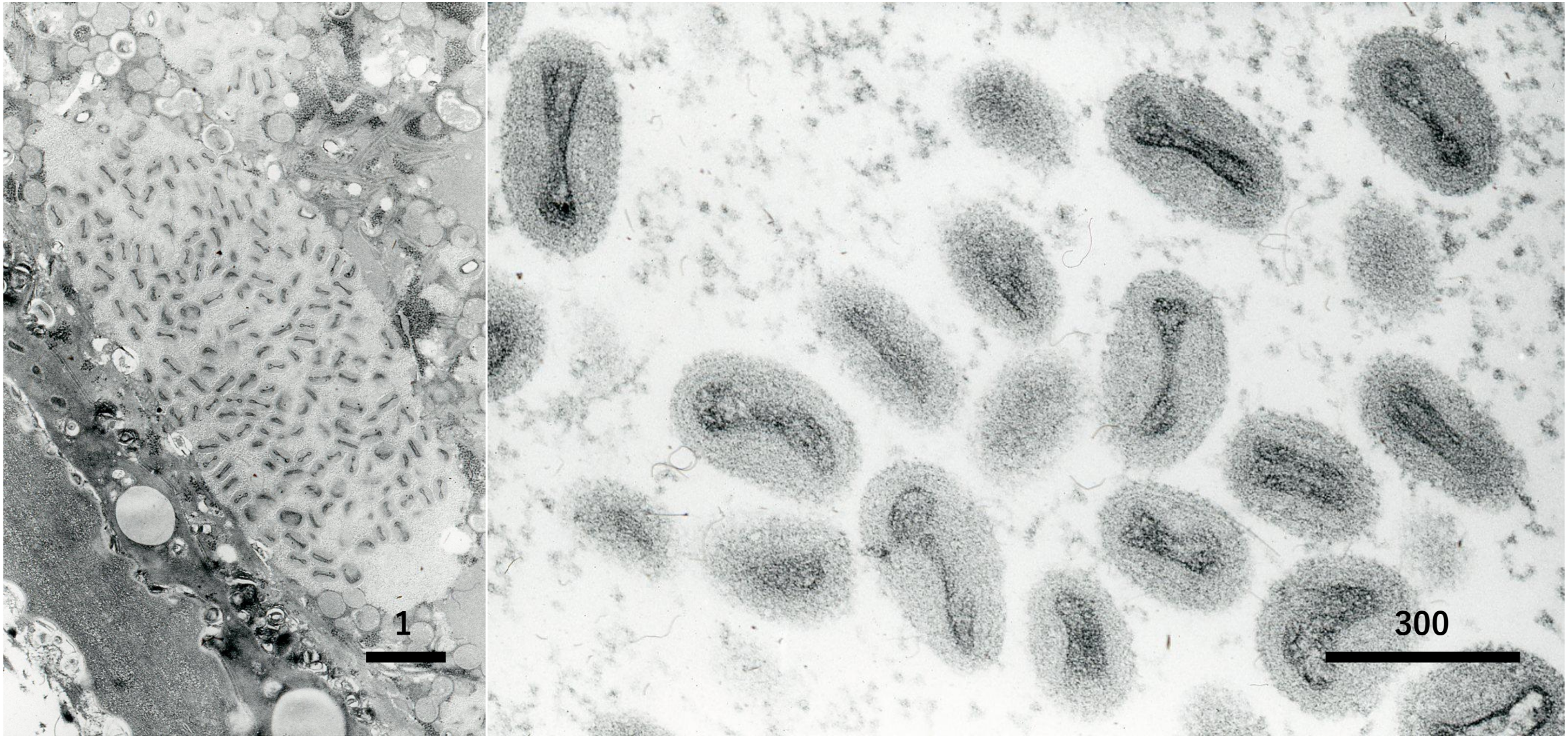




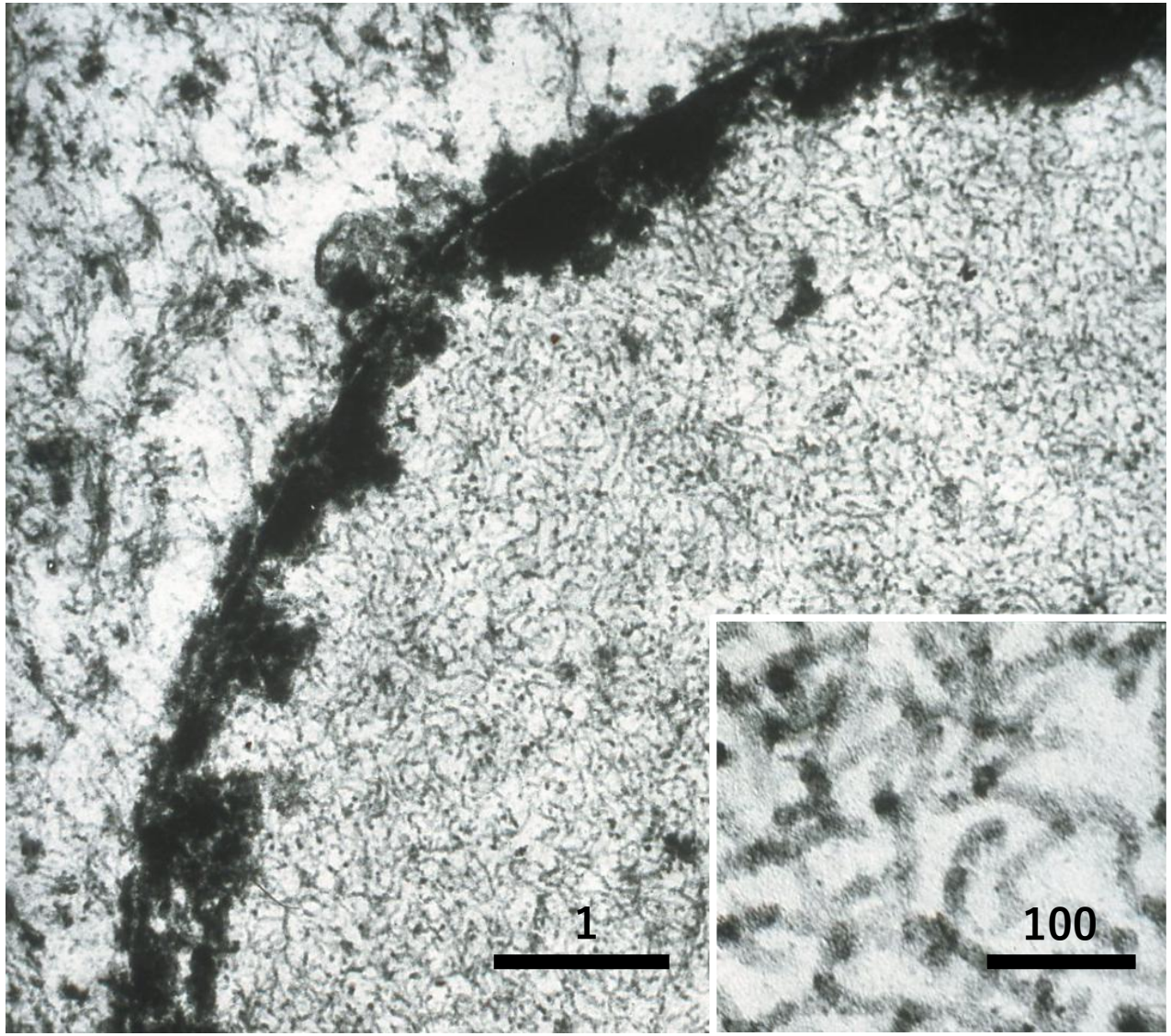
Adenovirus infection of the small bowel. A 10 y-o boy received bone marrow transplantation for treating ALL, and severe melena soon killed him. At autopsy, the small intestinal epithelial cells showed intranuclear inclusions. Formalin-fixed, paraffin-embedded sections were evaluated for EM study (TEM). The nucleus is filled with regularly arranged viral particles around 70 nm in size. Some particles lack the core (virions).



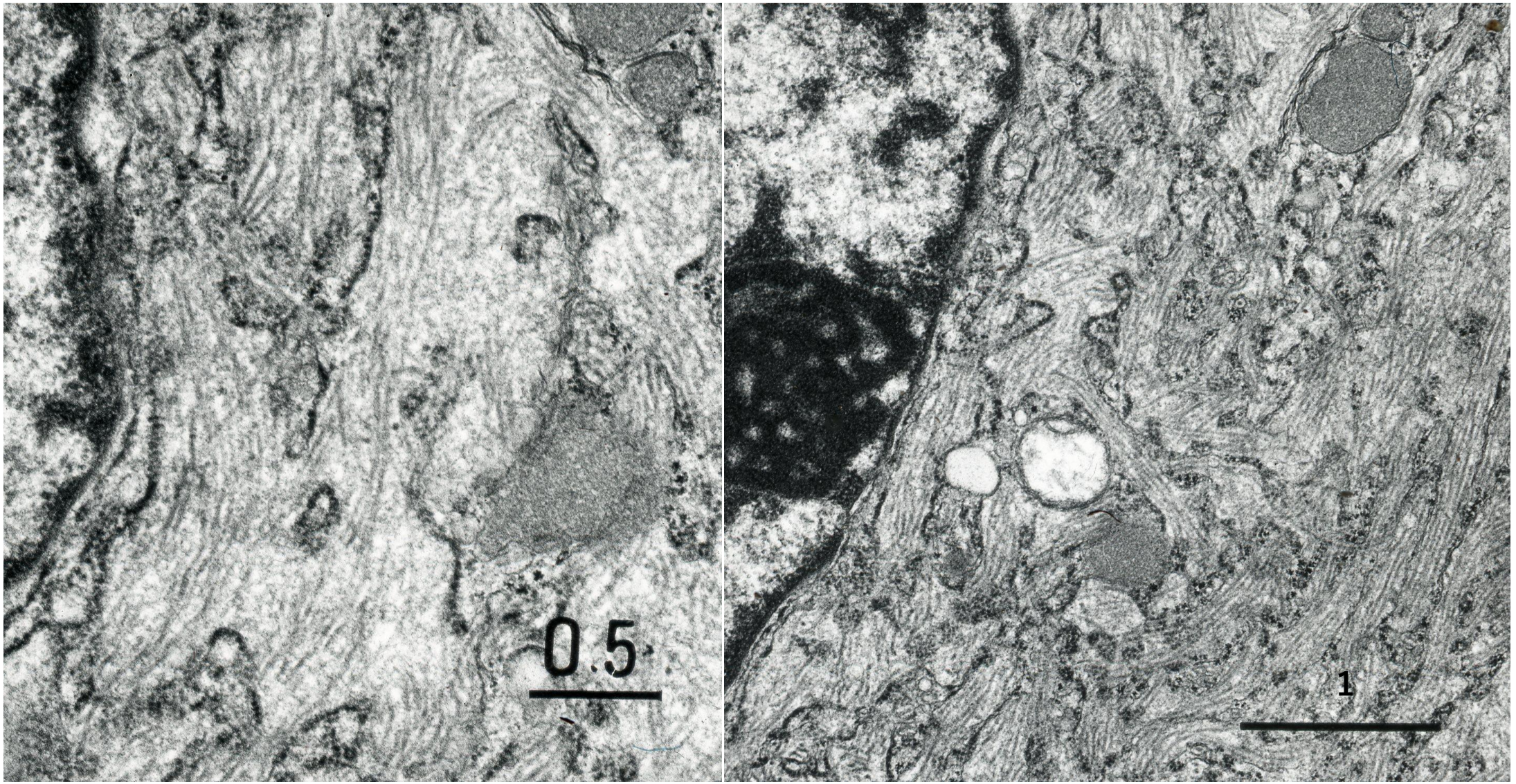
Adenovirus infection of the liver, manifesting fulminant hepatitis (TEM). A teenager body received bone marrow transplantation for treating AML. The hepatocyte contains an intranuclear viral inclusion. Regularly arranged viral particles measure around 70 nm.



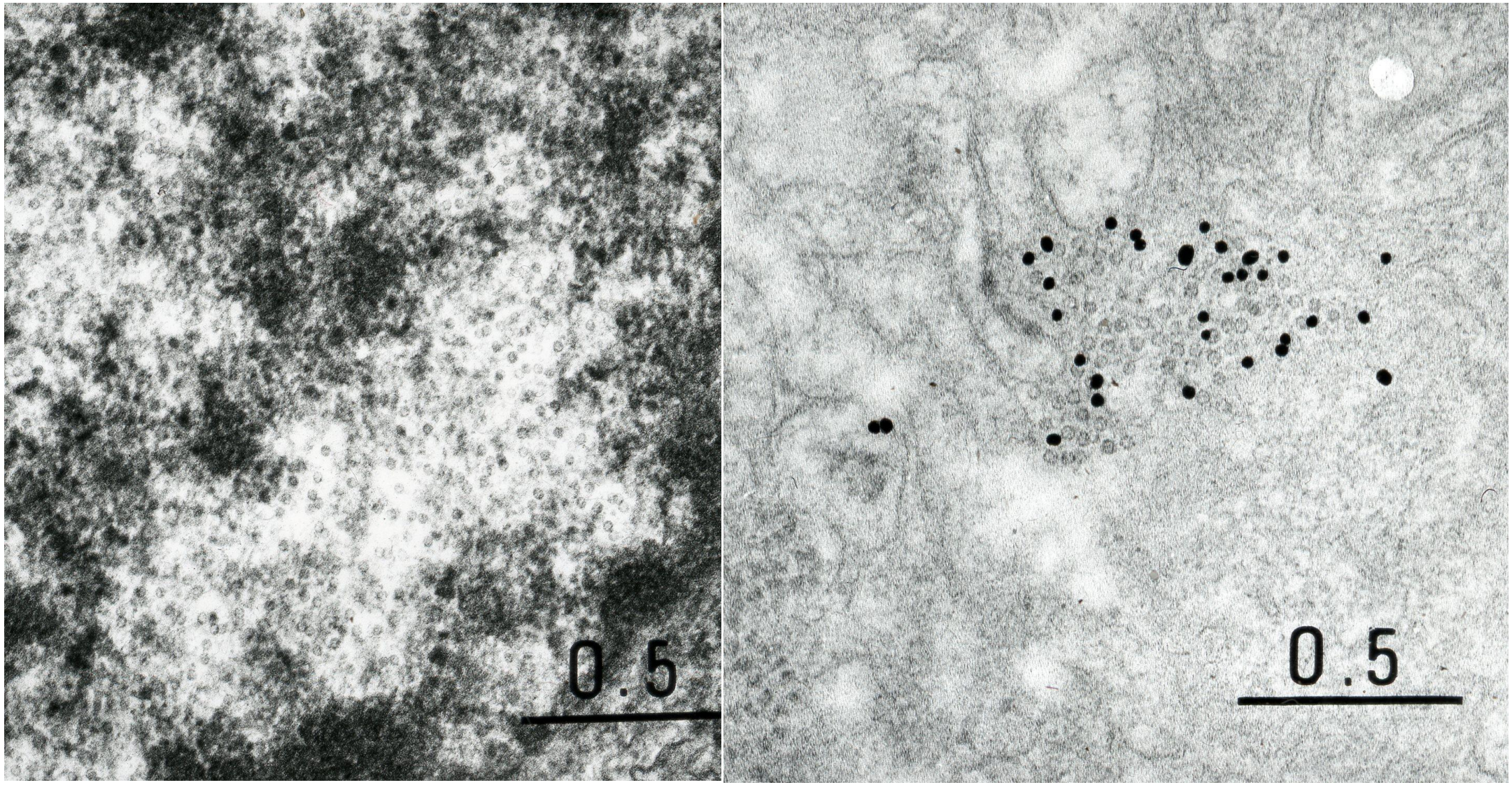
Molluscum contagiosum (TEM). The cytoplasm of the infected keratinocyte form a large inclusion body called the molluscum body. Molluscum virus is double-stranded DNA virus exceptionally to form cytoplasmic inclusion bodies. The viral particles are elliptical and large-sized (up to 300 nm in the axis), and consists of the outer envelope and the inner dumbbell-shaped electron-dense nucleoid. Their size is comparable with Chlamydia, the smallest bacterium.



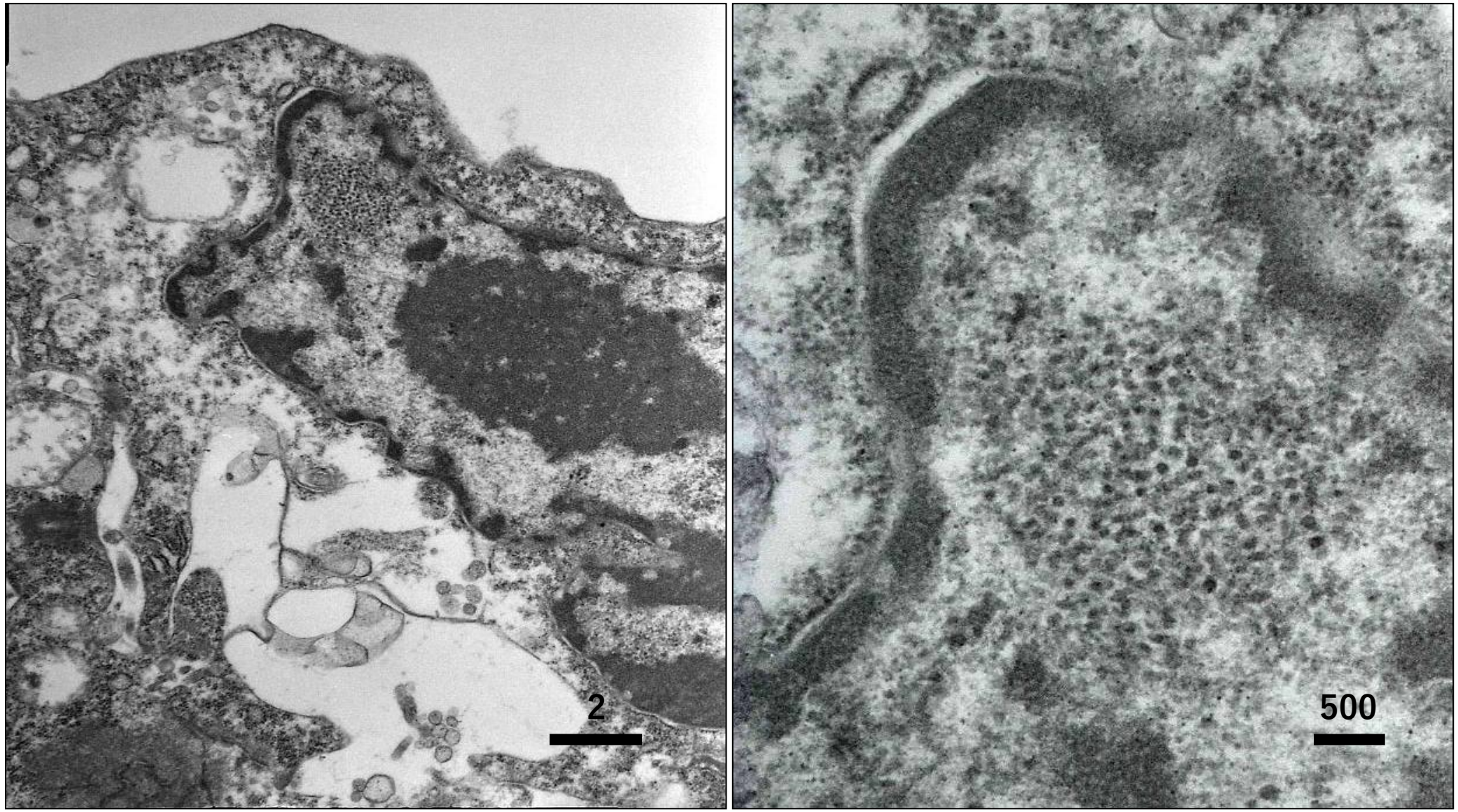
Subacute sclerosing panencephalitis (SSPE) (TEM). Measles virus persistently infects the oligodendrocyte to cause demyelination and reactive gliosis in the pediatric brain. Mental disturbance and myoclonus seizure are the main manifestations. Tubular and spiral nucleocapsids, 15 nm in diameter and 5 nm in the inner lumen size, are observed in the oligodendroglial intranuclear inclusion.



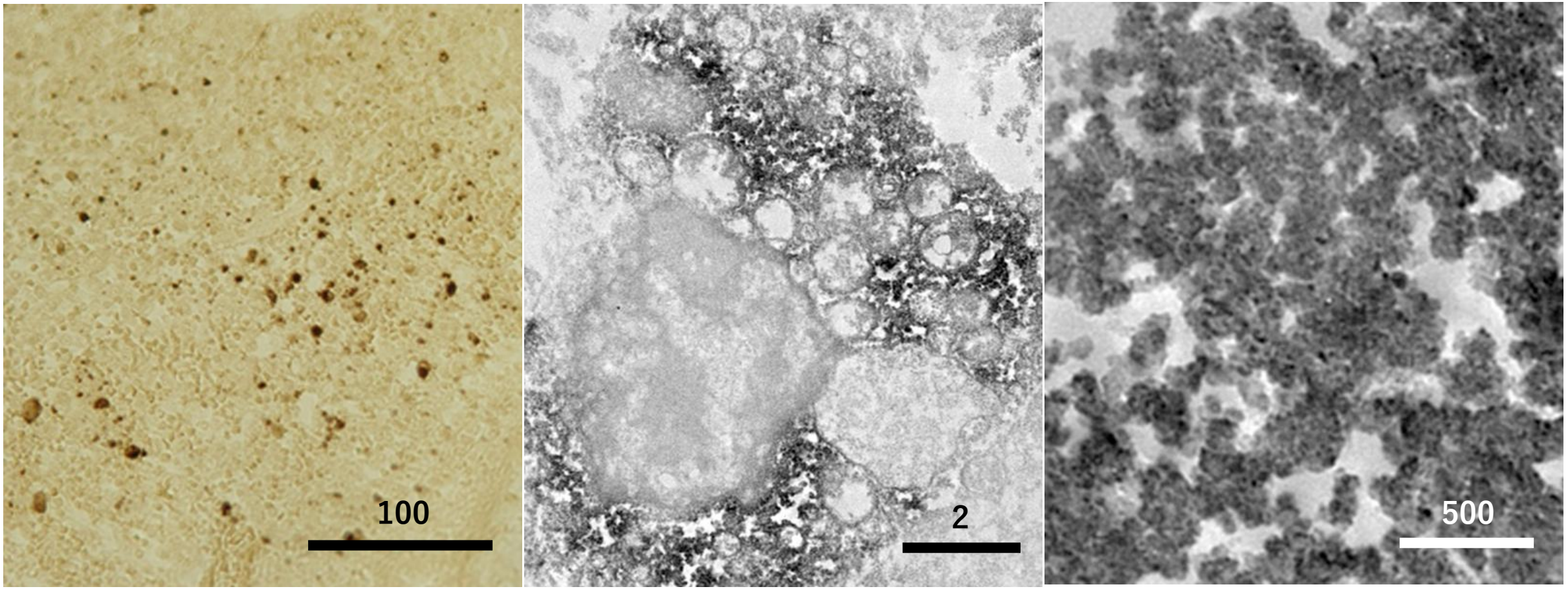
HBs antigen in a groundglass hepatocyte (TEM). Filamentous structures are filled in the cytoplasm, some in the cisterna of smooth endoplasmic reticulum. No viral particles are observed in the inclusion.



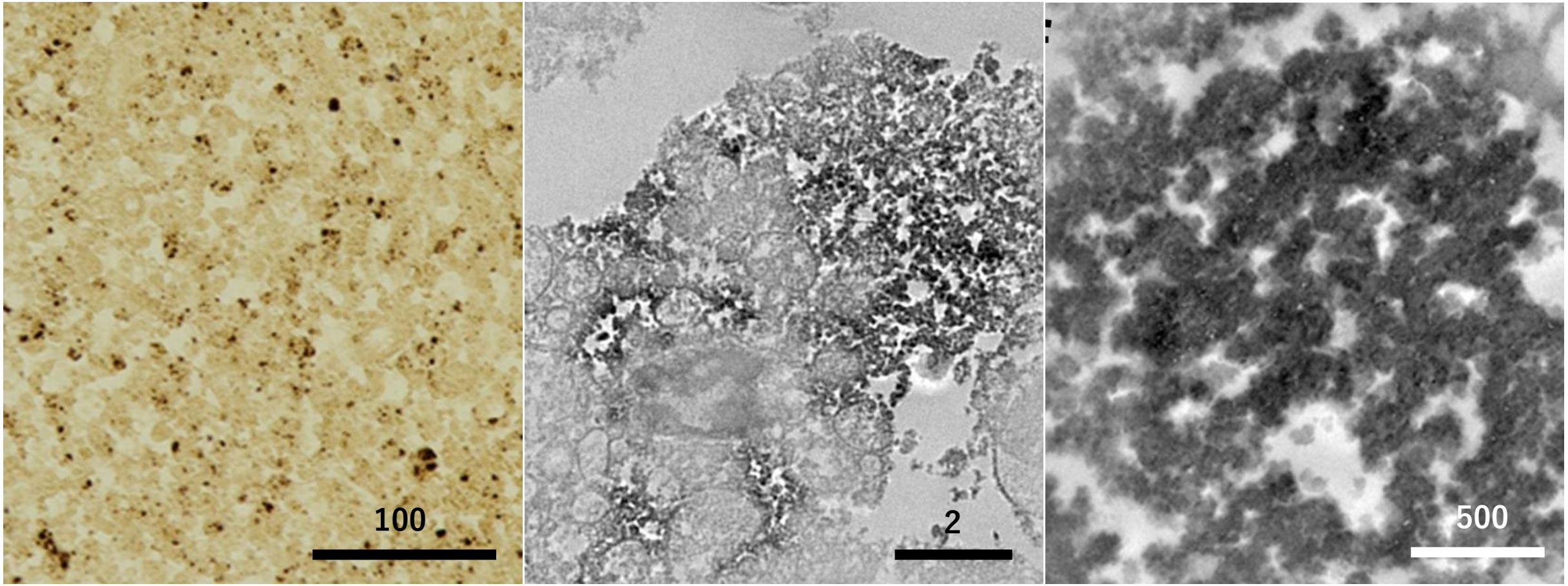
HBc antigen in the sanded nucleus in chronic active type B hepatitis (left: TEM, right: post-embedding immunoelectron microscopy for HBc antigen using the immunogold method (the grain size = 20 nm). Core particles, around 25 nm in size, form an intranuclear inclusion body, and are immunoreactive for HBc antigen.



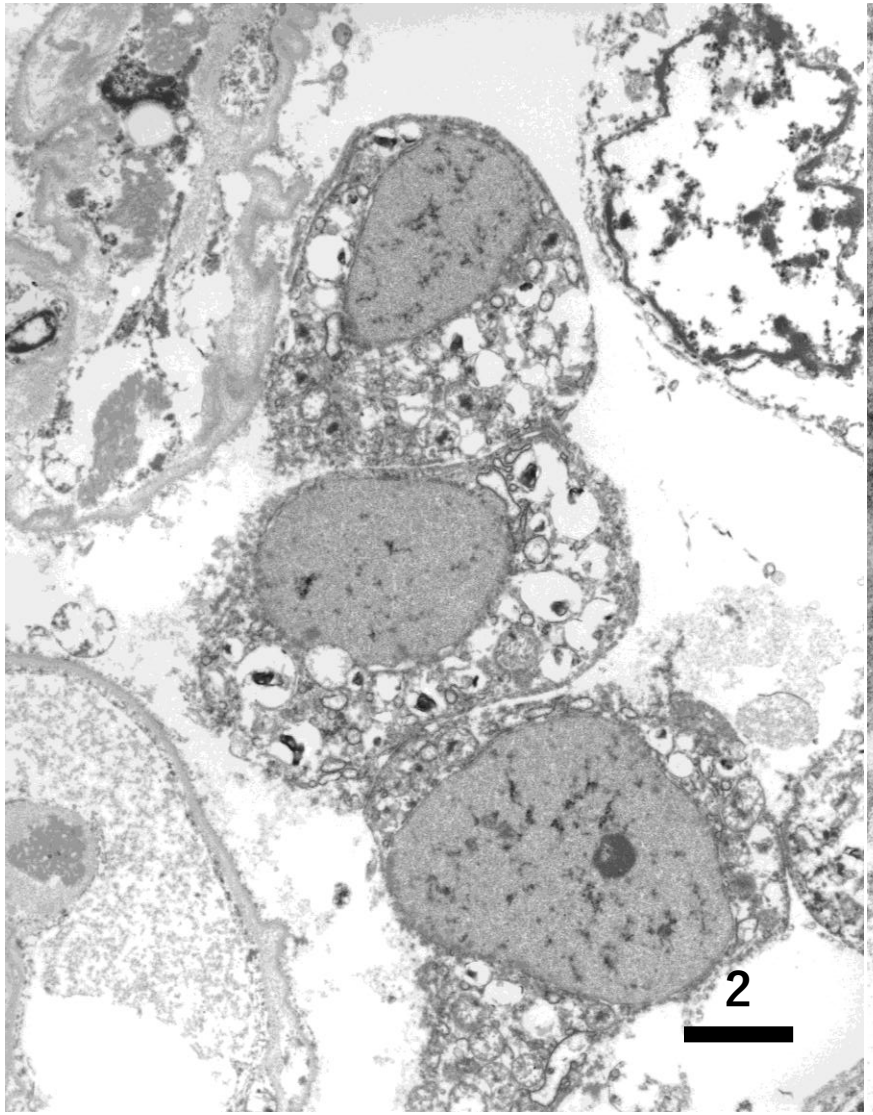
Porcine influenza virus A, H1N1 infection with diffuse alveolar damage in 2009 (TEM).
An intranuclear inclusion of the viral particles is observed in the alveolar epithelial cell.

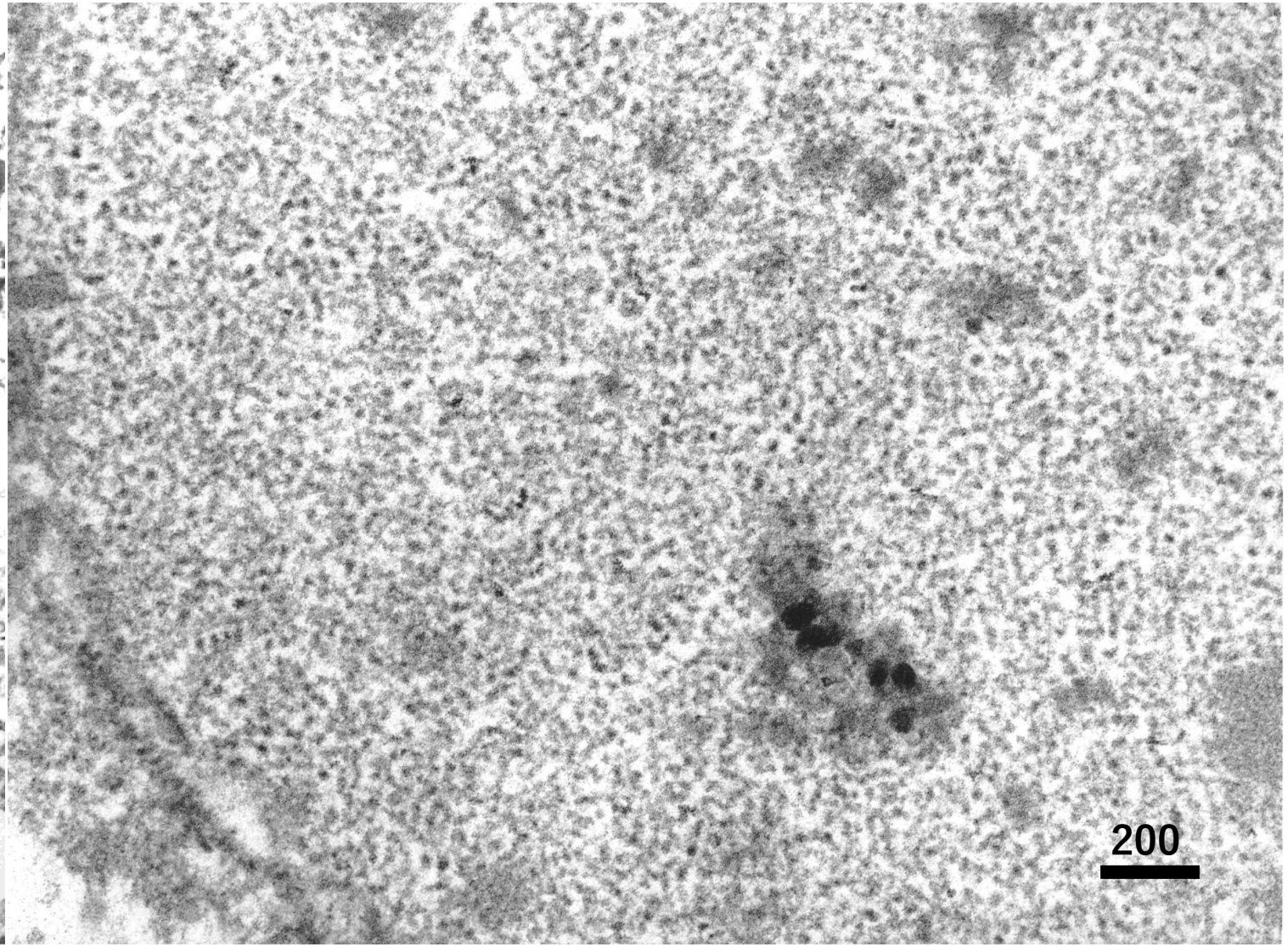


Severe fever thrombocytopenia syndrome (SFTS) virus infection in the splenic red pulp. Immunostaining with a mouse monoclonal antibody. Left: light microscopic findings, center & right: pre-embedding immunoelectron microscopy. The SFTS virus infect the cytoplasm of splenic macrophages. Round-shaped viral particles, around 100 nm in diameter, are visualized. **Ref**. Matsui T, et al. Coated glass slides TACAS are applicable to heat-assisted immunostaining and in situ hybridization at the electron microscopy level. Acta Histochem Cytochem 2015; 48(5): 153-157. doi: 10.1267/ahc.15012

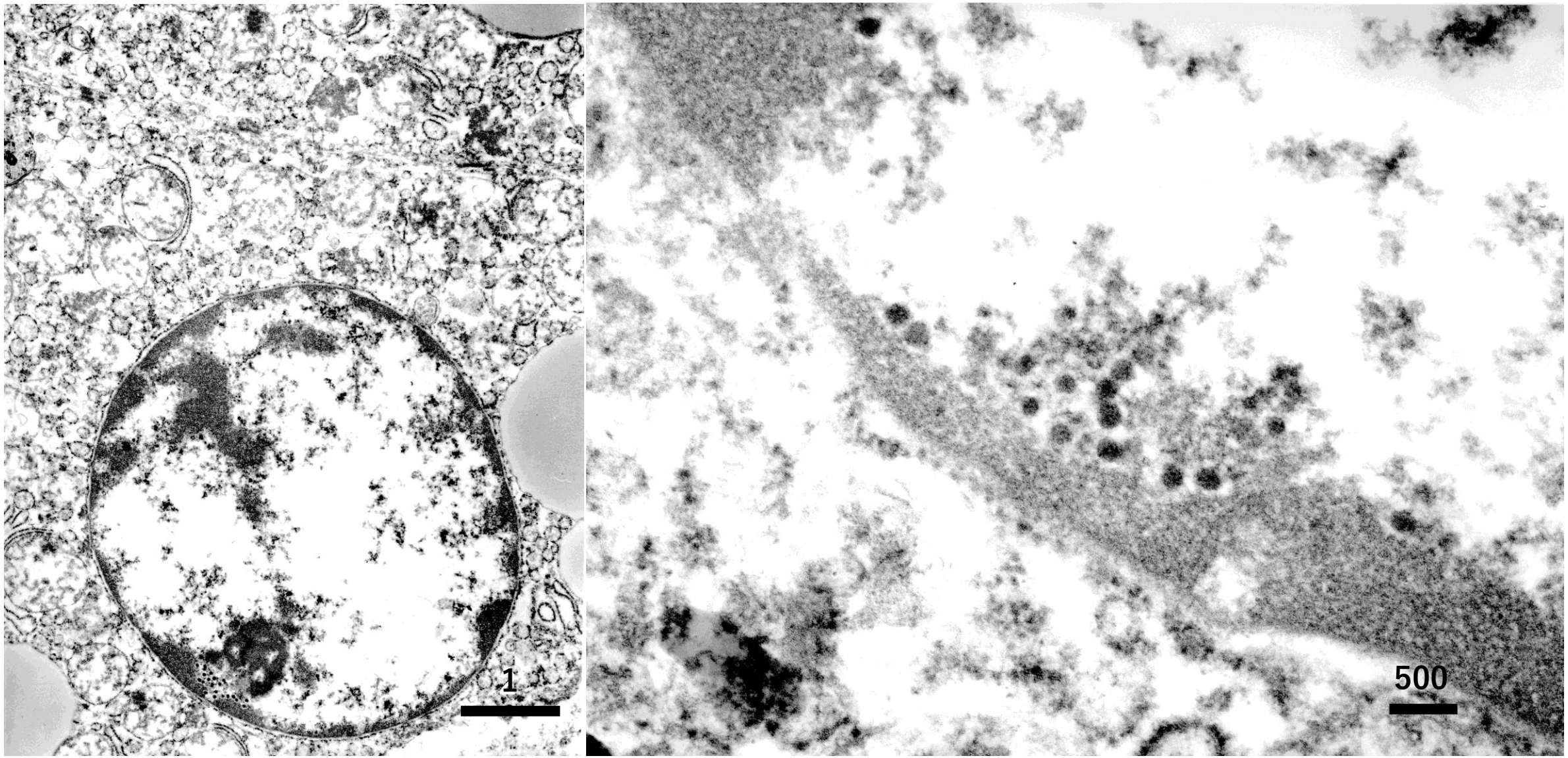


Severe fever thrombocytopenia syndrome (SFTS) virus infection in the splenic red pulp. *In situ* hybridization (ISH) for SFTS RNA with AT tailed antisense cocktail probes. Left: light microscopic findings, center & right: pre-embedding ISH. The SFTS virus infect the cytoplasm of splenic macrophages. Round-shaped viral particles, around 100 nm in diameter, are visualized. **Ref**. Matsui T, et al. Coated glass slides TACAS are applicable to heat-assisted immunostaining and in situ hybridization at the electron microscopy level. Acta Histochem Cytochem 2015; 48(5): 153-157. doi: 10.1267/ahc.15012

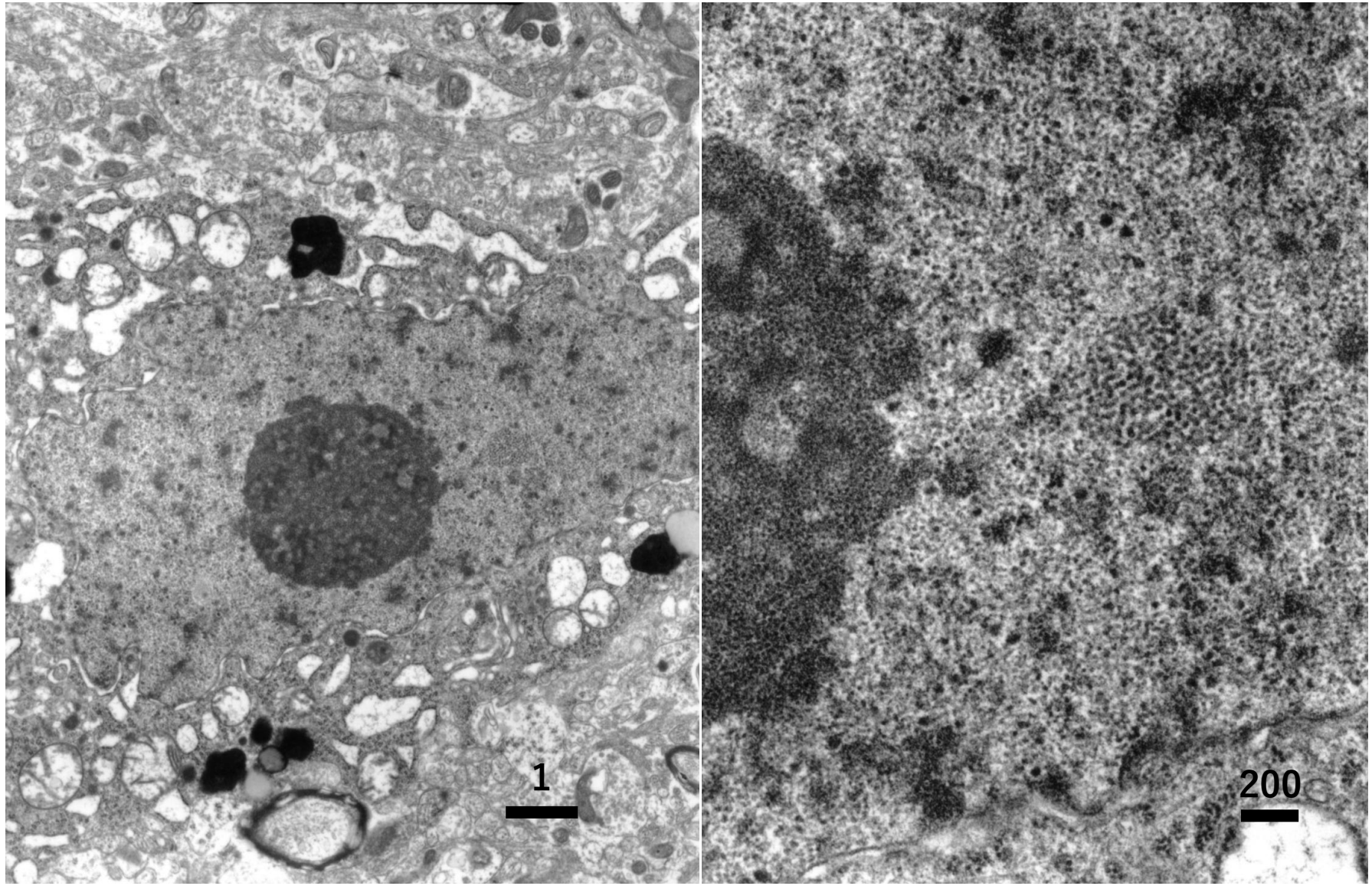




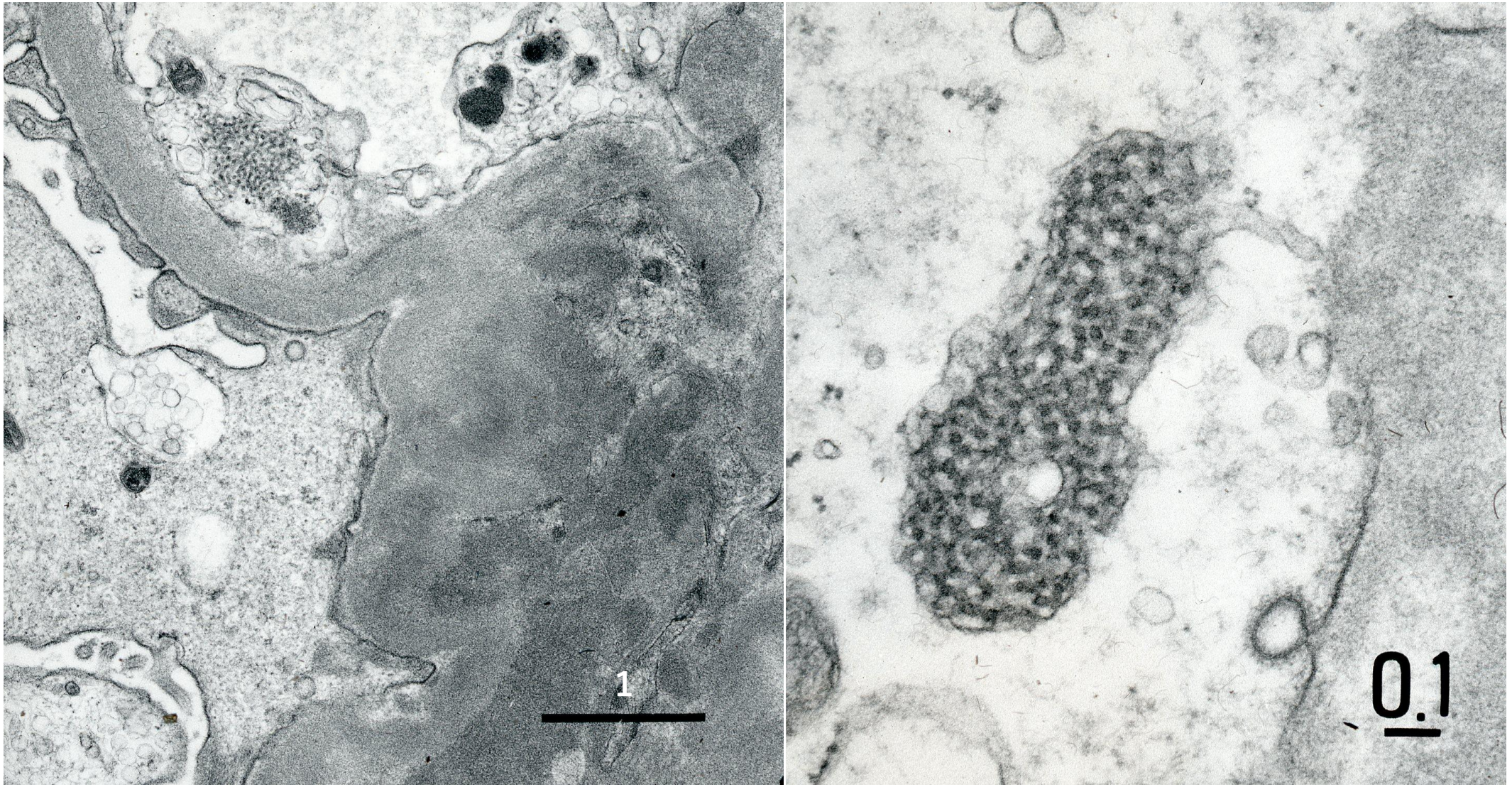
Paramyxovirus infection manifesting lethal acute interstitial pneumonia seen in a 72 y-o male patient (TEM). Hyperplastic type 2 pneumocytes show intranuclear viral inclusions. Small round to rod-shaped viral particles, suggesting infection of paramyxovirus, occupy the nuclear matrix.



Intussusception seen in a 4 months-old boy (TEM). In an epithelial cell of the terminal ileum, virus-like small-sized rounded particles are focally seen in the nucleus. The etiology of intussusception is unknown, but many infants have a history of viral infection (such as flu) just before onset.



Non-bacterial meningitis seen in a 47 y-o male patient (TEM). In the brain biopsy specimen, viral inclusions are focally seen in the nucleus of a meningothelial cell, strongly suggesting a viral etiology.



Lupus nephritis with virus-like particles in the endothelial cell (TEM). Renal biopsy from a 36 y-o female patient with active SLE demonstrates tubuloreticular viral inclusion-like structures in the cytoplasm of the endothelial cell. The viral nature has not been established, but their presence is of diagnostic value for lupus nephritis.