

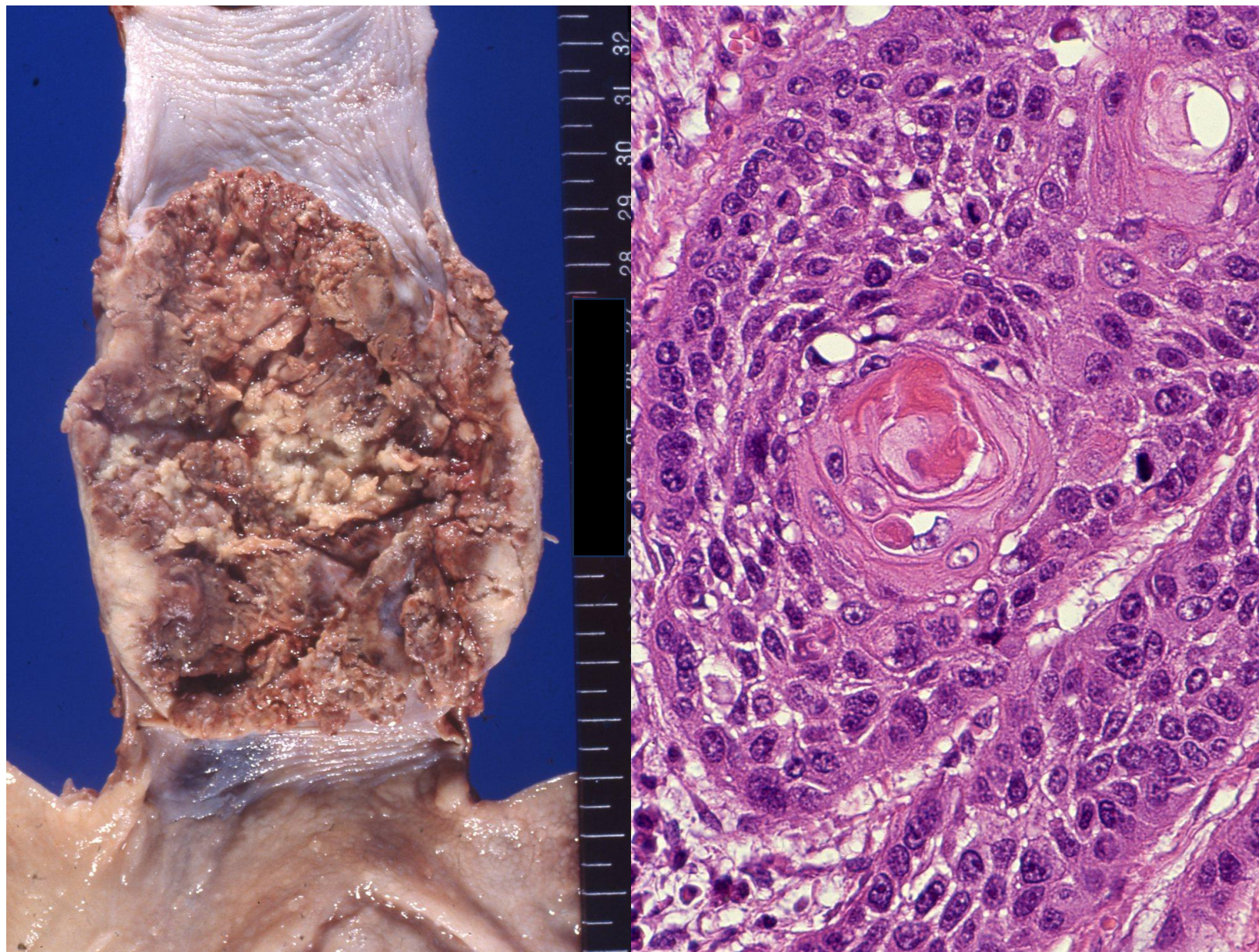
Differences in the incidence of neoplastic and non-neoplastic disorders between western countries and Japan

The occurrence of the disease is significantly influenced by both genetic and environmental factors. As the looks and languages are different, the susceptibility to illness is significantly different between the Japanese and people in western countries. We often call this difference as constitution among the races. Some diseases are frequently seen among the Japanese, while the other diseases are very rare in Japan. For example, the high incidence of gastric cancer in Japan is closely related to high-rate *Helicobacter pylori* infection in the gastric mucosa, and very high incidence of nasal and conjunctival allergy against Pollens of the Japanese Cedar tree is intimately linked to the environmental factor (the Japanese forest is very rich in this Japanese-proper tree). The relatively low incidence of color vision deficiency and cystic fibrosis in Japan is based on the genetic factors.

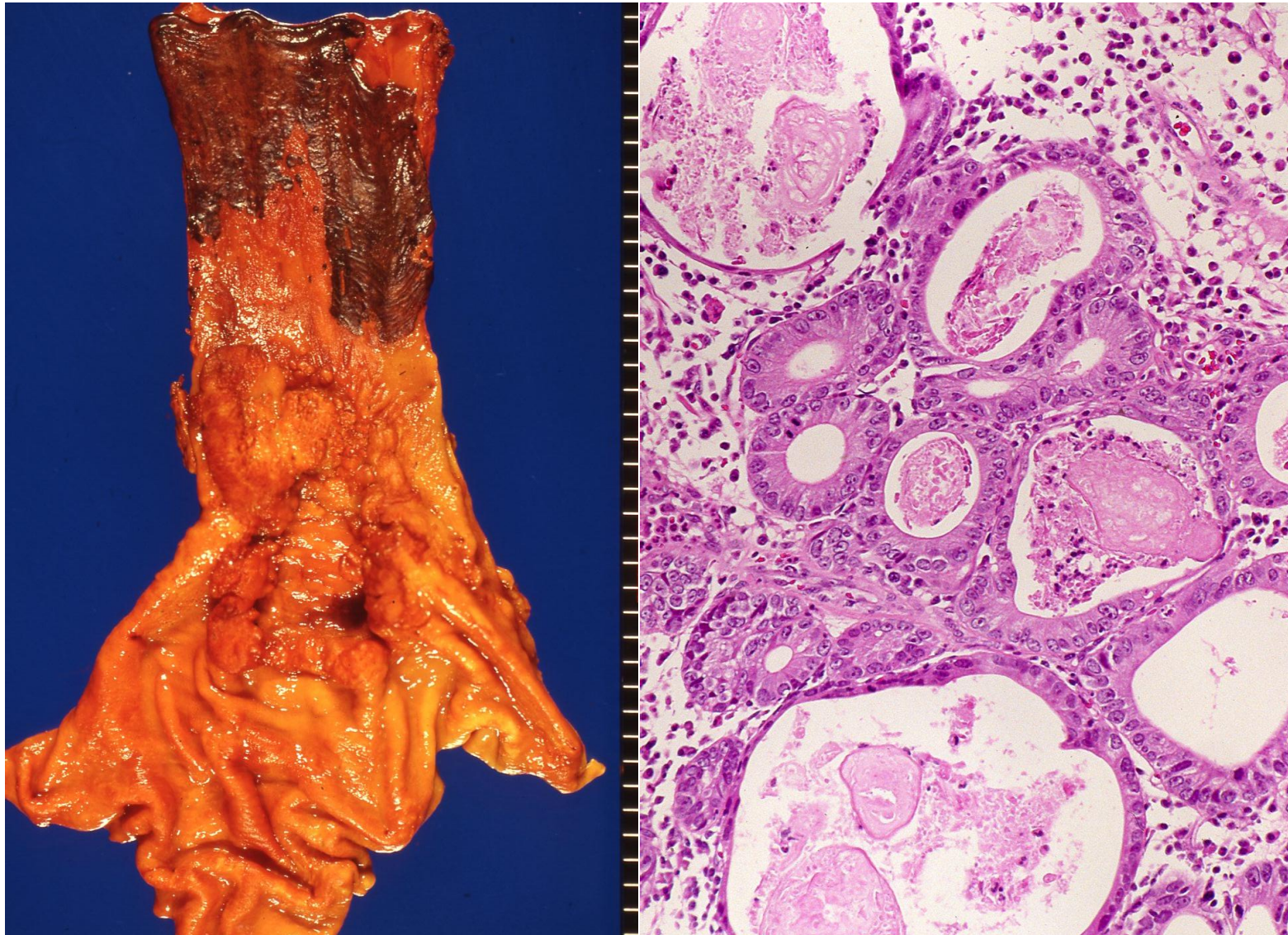
Ref.: Okuda M. The big difference of the constitution for diseases between the Japanese and western people. The appropriate prevention of cancer and lifestyle diseases based on the scientific data. Bluebacks, Kodansha, 2026 (240 pages), ISBN 978-4062579971 (in Japanese)

Incidence of diseases in the digestive tract

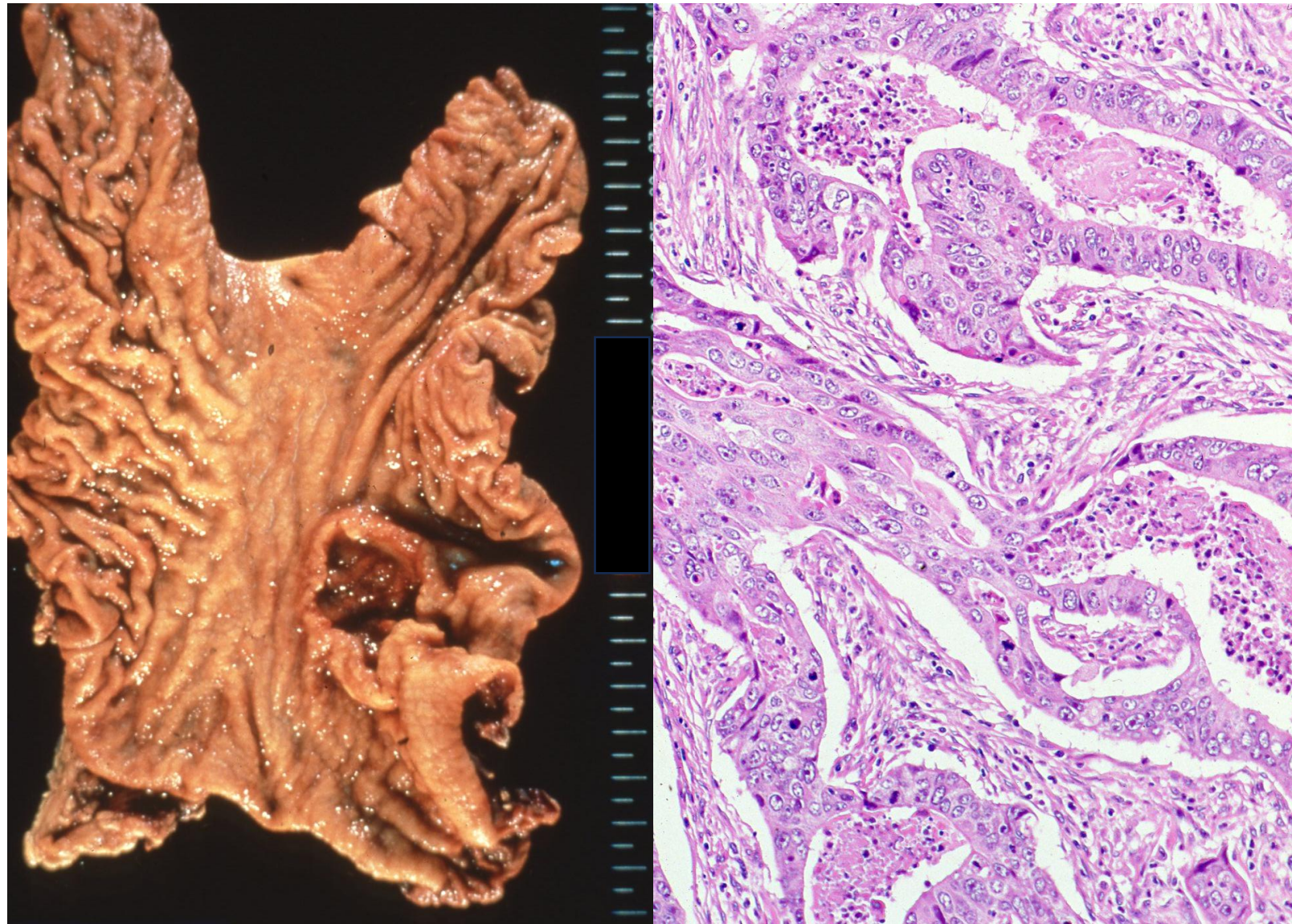
- 1) High incidence of squamous cell carcinoma of the esophagus
- 2) Low incidence of long-segment Barrett's esophagus
- 3) High incidence of gastric cancer in Japan
- 4) High incidence of anal gland carcinoma in Japan
- 5) High incidence of rectal carcinoid in Japan
- 6) High incidence of hepatocellular carcinoma in Japan
- 7) Individuals with low alcohol dehydrogenase activity are common among the Japanese



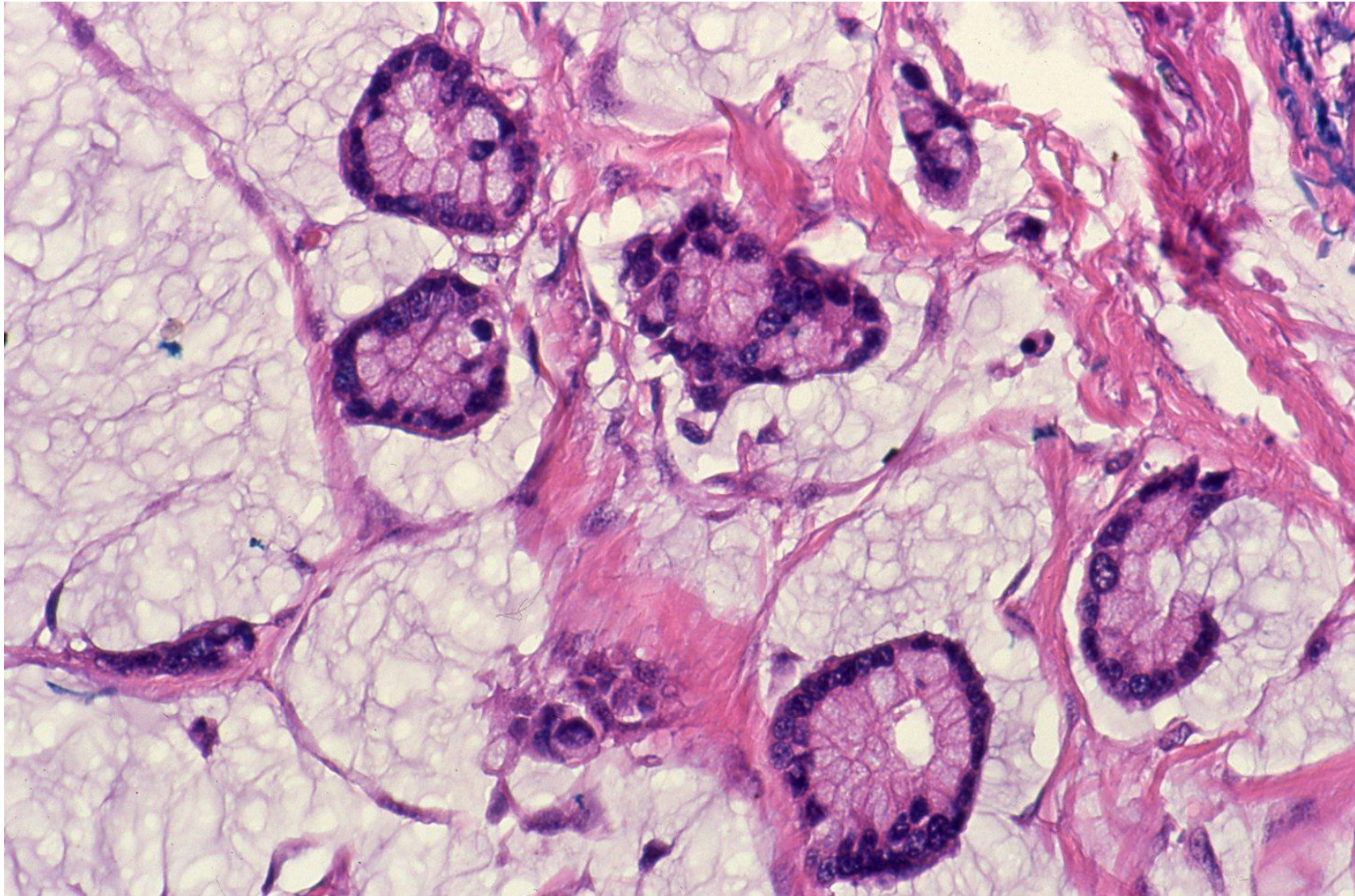
In Japan, most of the esophageal cancer belong to squamous cell carcinoma. The incidence of long-segment Barrett's esophagus is low in Japan, and esophageal adenocarcinoma is relatively infrequent.



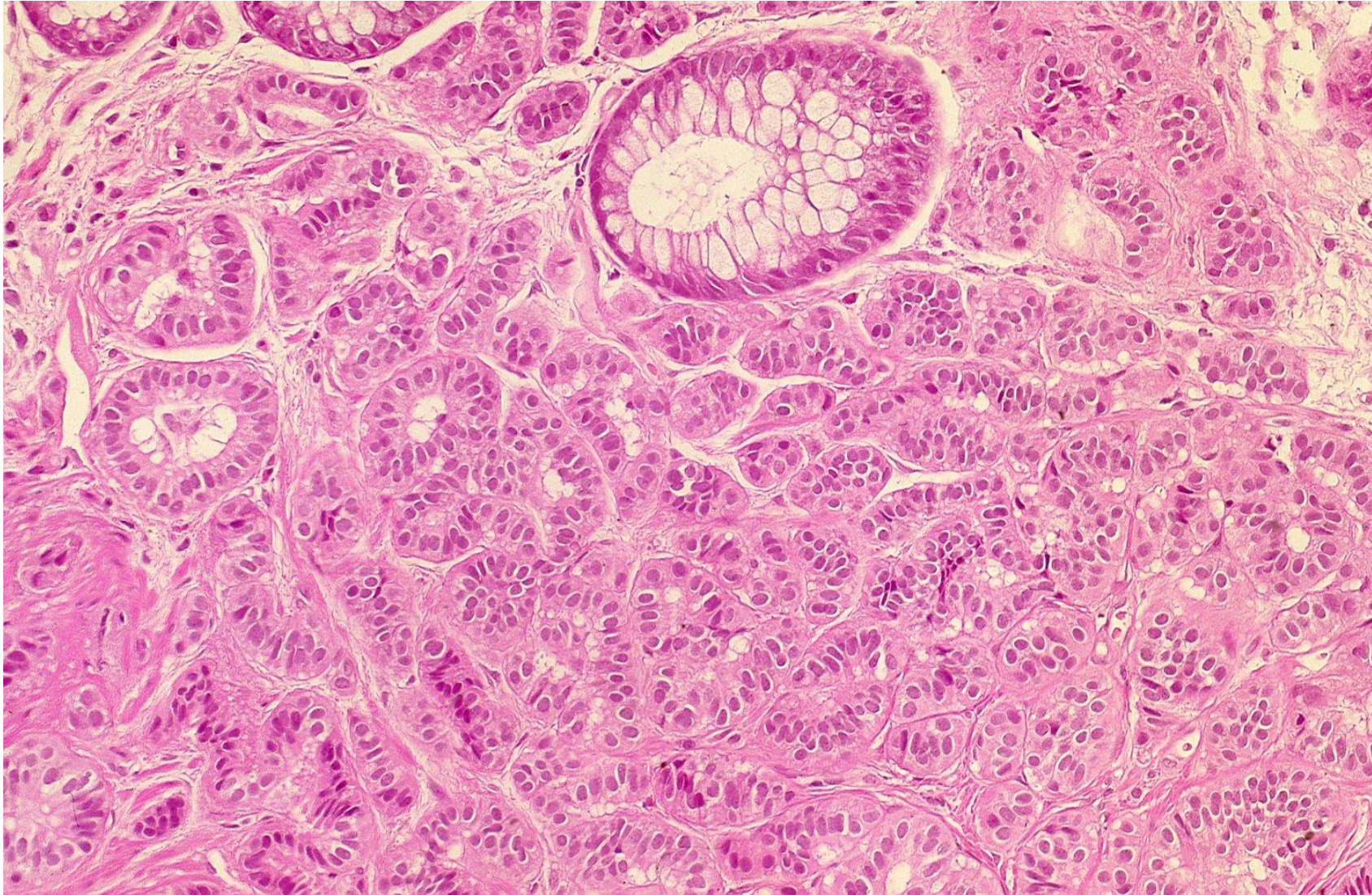
Adenocarcinoma occurring in long-segment Barrett's esophagus. Well-differentiated tubular adenocarcinoma (right: H&E) occurred at the esophagogastric junction in Barrett's mucosa. Normal esophageal squamous mucosa is stained black by Lugol dye (left: gross appearance).



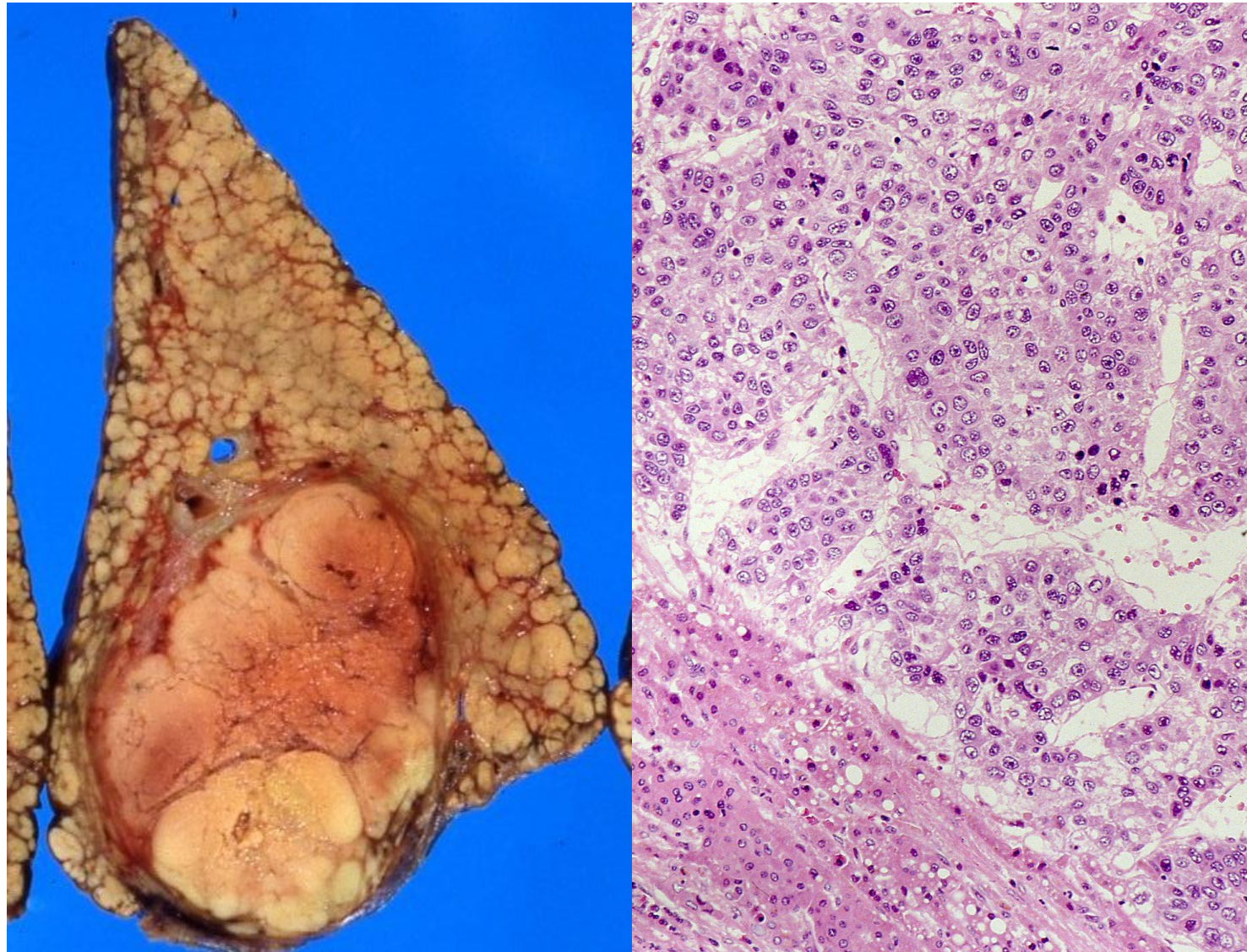
The high incidence of gastric cancer in Japan is closely related to the high prevalence of *Helicobacter pylori*-induced chronic gastritis.



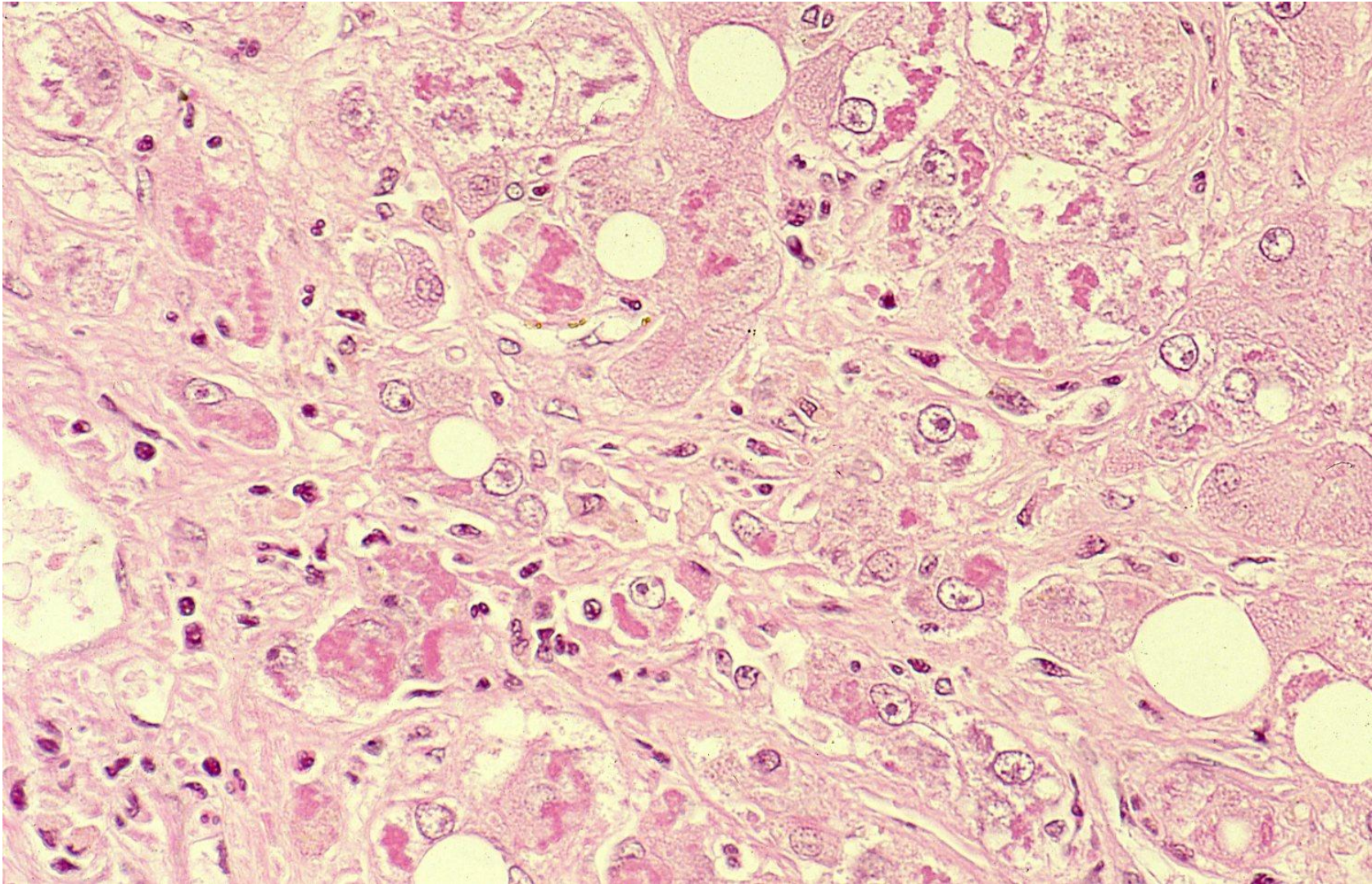
Anal gland adenocarcinoma is common in Japan, and this is related to the high incidence of anal fistula (infection of the anal gland). H&E



Rectal carcinoid of hind gut type is the commonest form of the neuroendocrine tumors among the Japanese. Carcinoid of mid-gut origin arising from the vermiform appendix and terminal ileum is infrequent. H&E



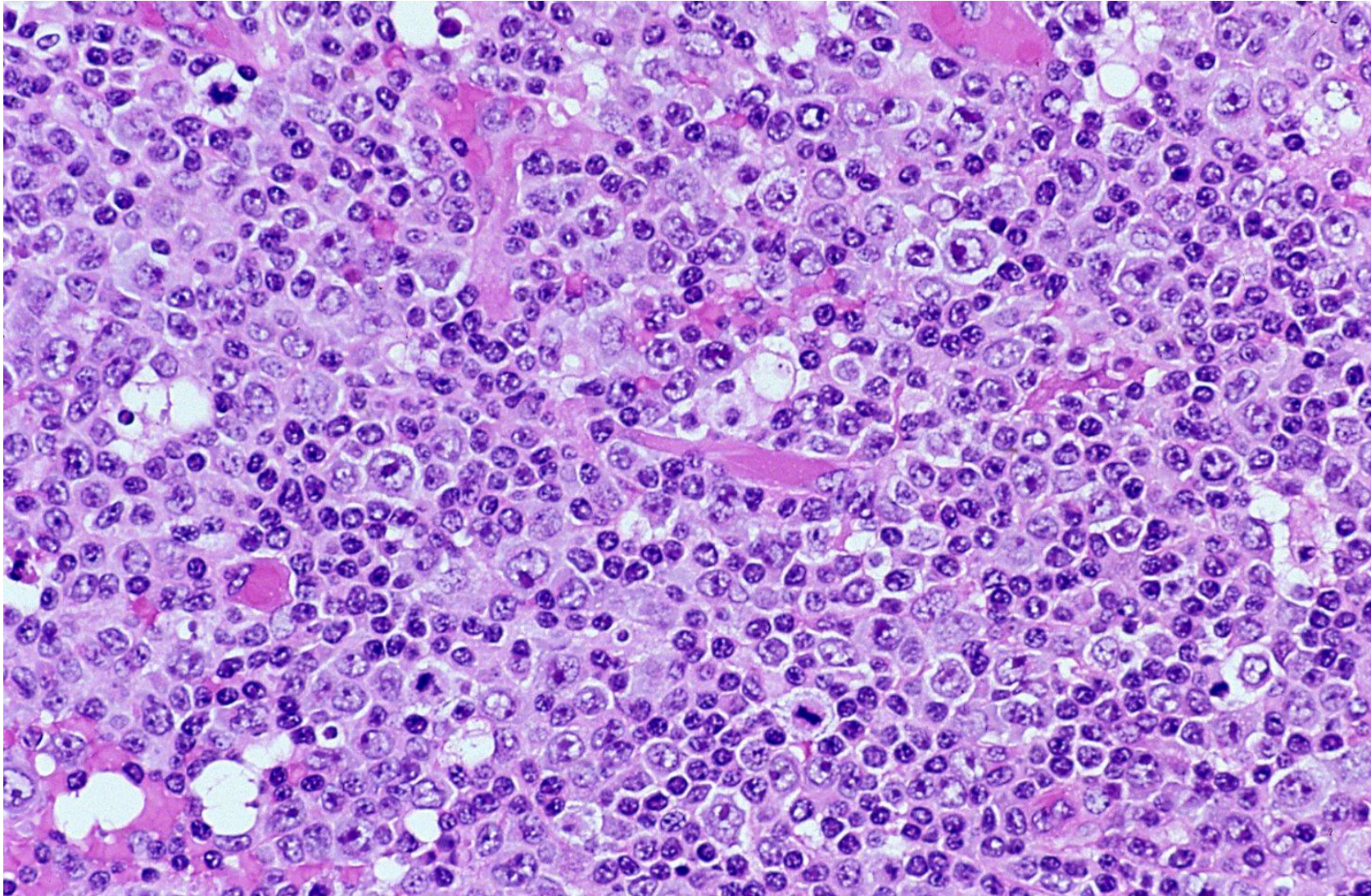
The incidence of hepatocellular carcinoma is high in Japan. This is related to the relatively high rate of HCV-induced liver cirrhosis among the Japanese.



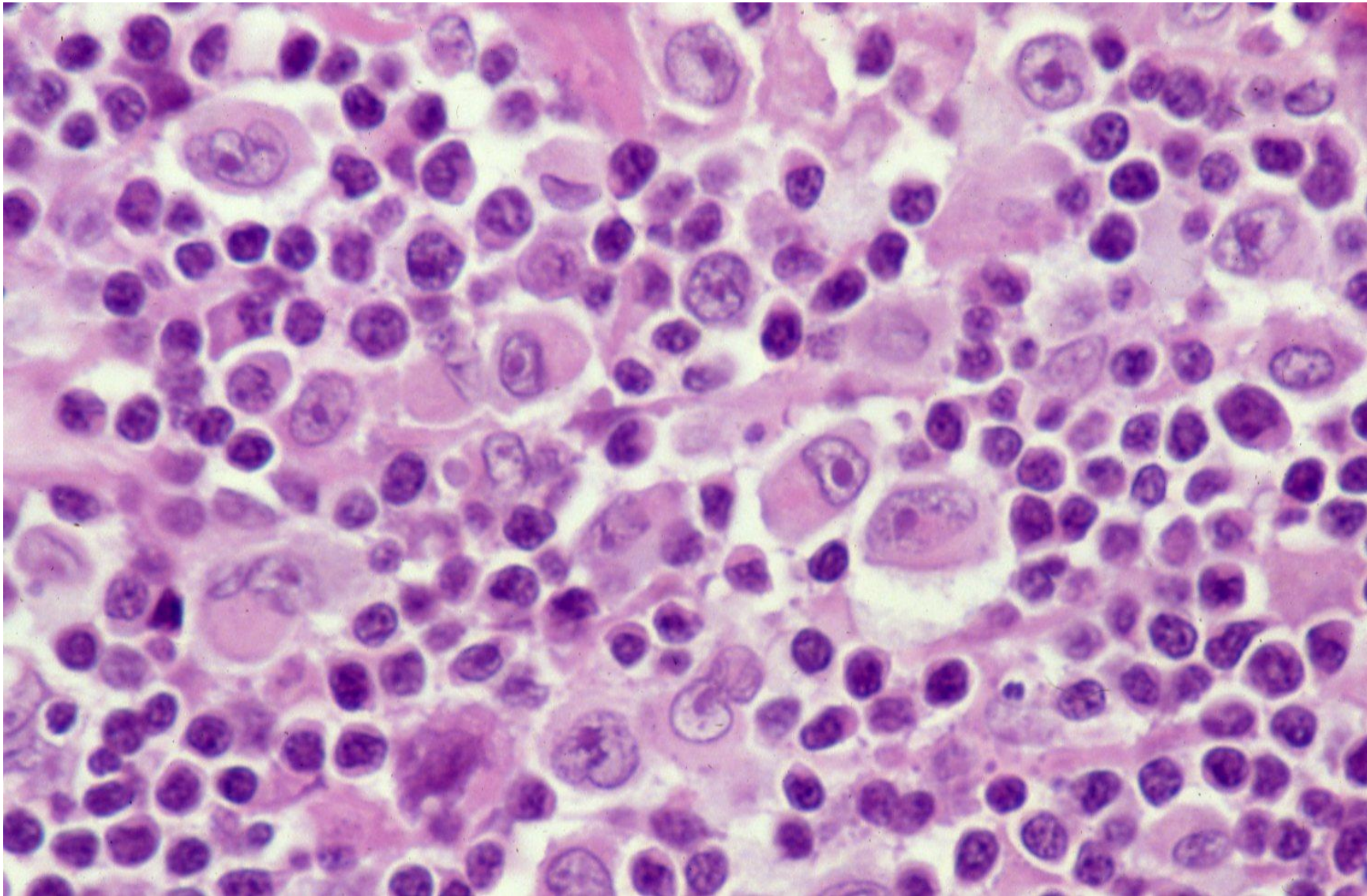
The incidence of alcoholic hepatitis is relatively low in Japan. This is related to the fact that many Japanese people have low alcoholic dehydrogenase activity in the hepatocyte, who hates alcohol drinking. H&E (alcoholic hepatitis with Mallory body formation)

Peculiar locality of the incidence of EBV-related diseases

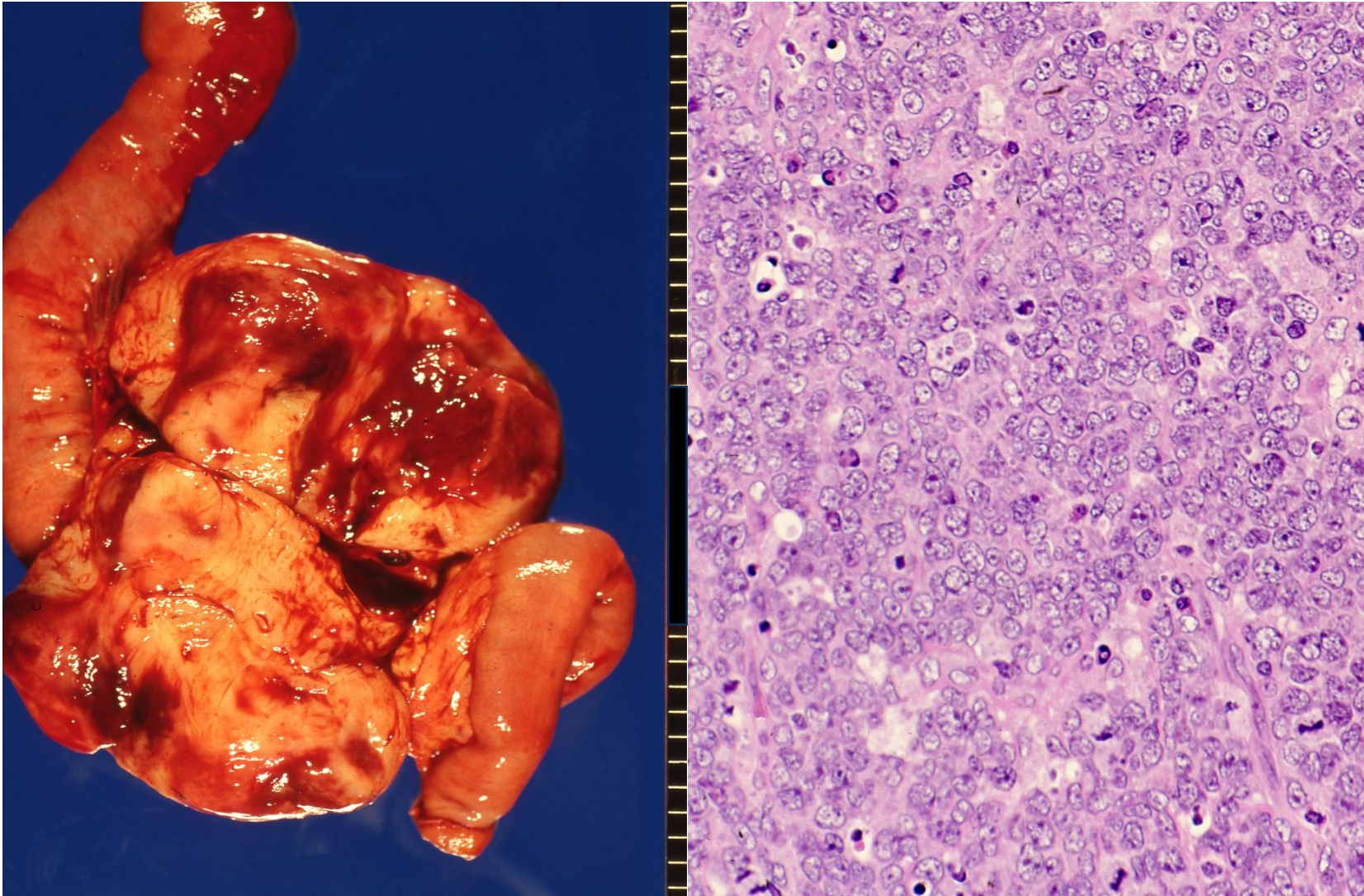
- a) infectious mononucleosis is common in western countries.
- b) Hodgkin's lymphoma is common in western countries.
- c) Burkitt's lymphoma is common in African children.
- d) nasal NK/T lymphoma is common in eastern Asia, including Japan
- e) pyothorax-related large B-cell lymphoma is common in Japan.
- f) High incidence of methotrexate-associated lymphoproliferative disorder in Japan
- g) nasopharyngeal carcinoma is common among the Chinese, particularly in the Canton and Hong Kong regions.



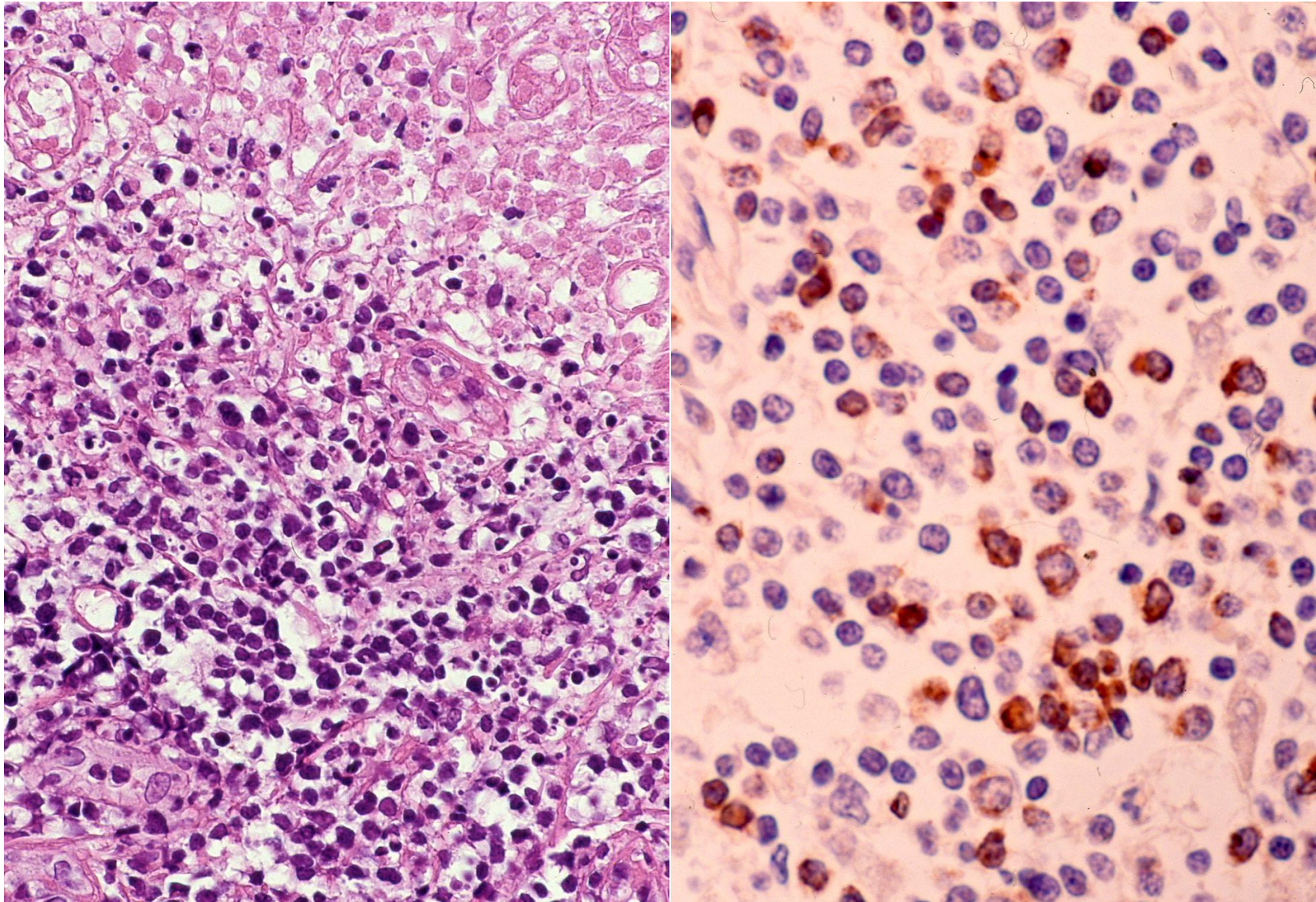
A biopsied lymph nodal lesion of Infectious mononucleosis (IM). EBV-provoked activation of lymphocytes is evident. IM is infrequent among the Japanese because of early exposure to EBV in infancy. H&E



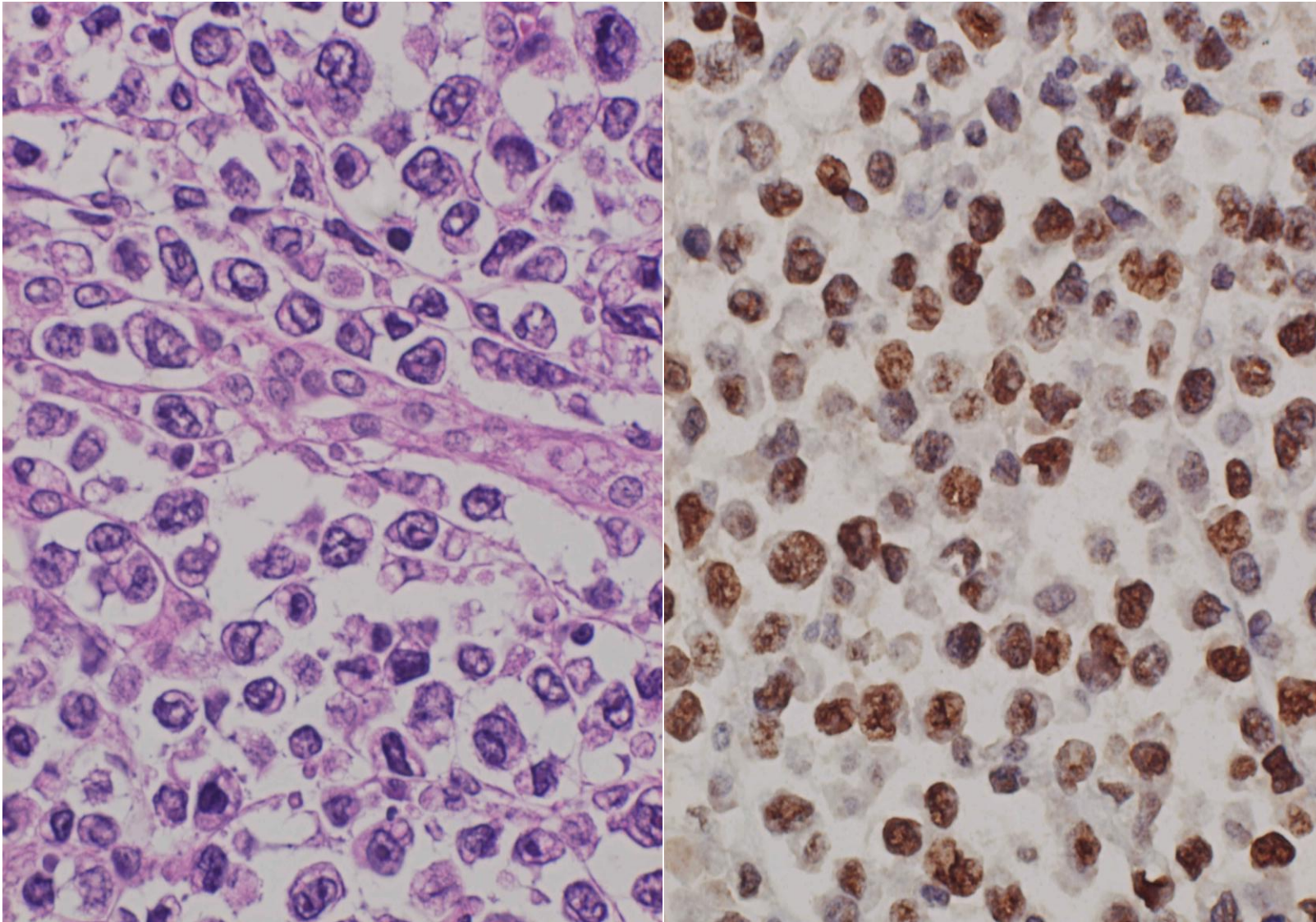
Hodgkin's lymphoma is relatively infrequent in Japan. Most of the malignant lymphomas in Japan are categorized in non-Hodgkin's lymphomas. H&E



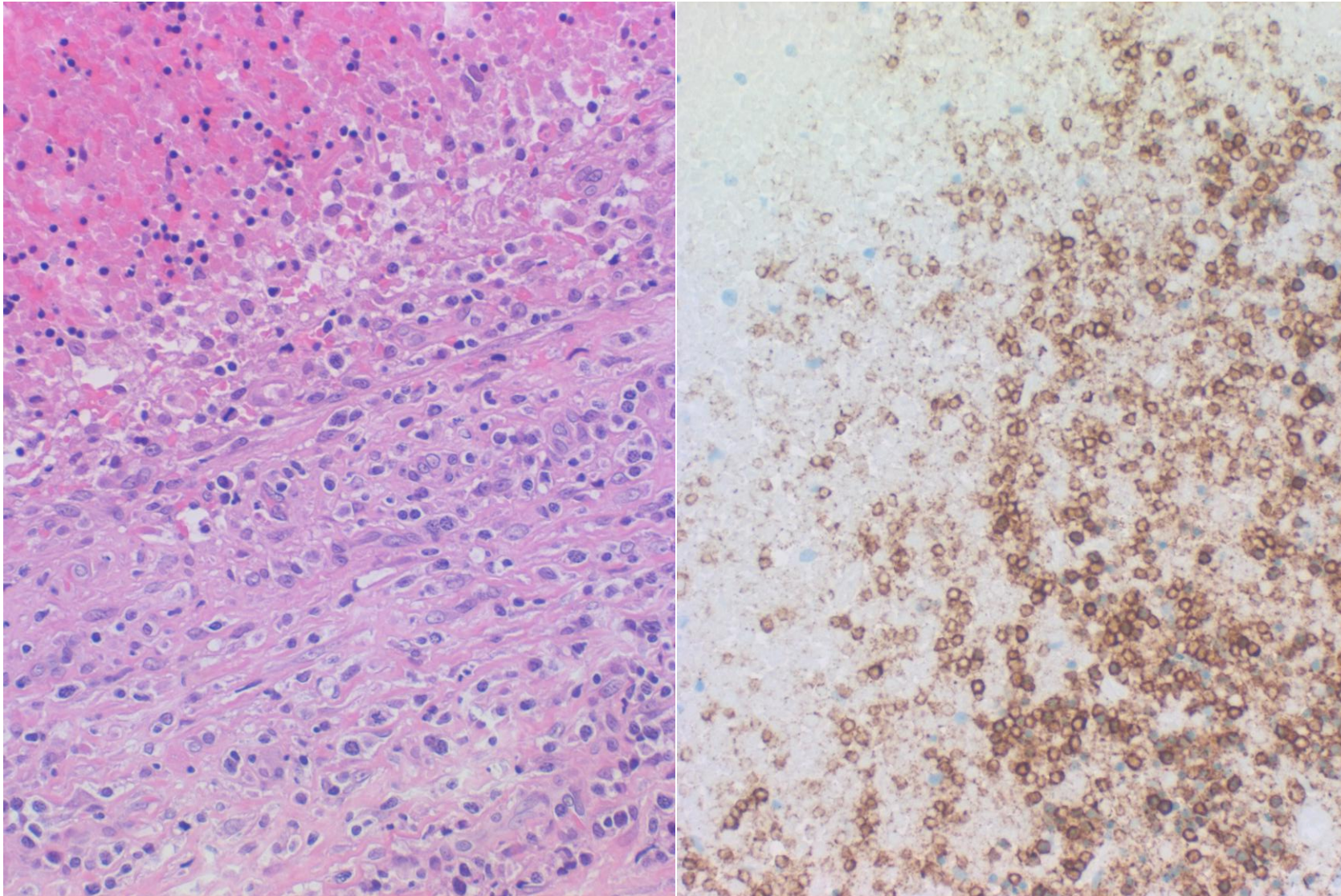
Burkitt lymphoma of the ileum of a Japanese child. Most Burkitt lymphomas with starry sky appearance are extranodal in location. Facial Burkitt common in Africa is rare in Japan.



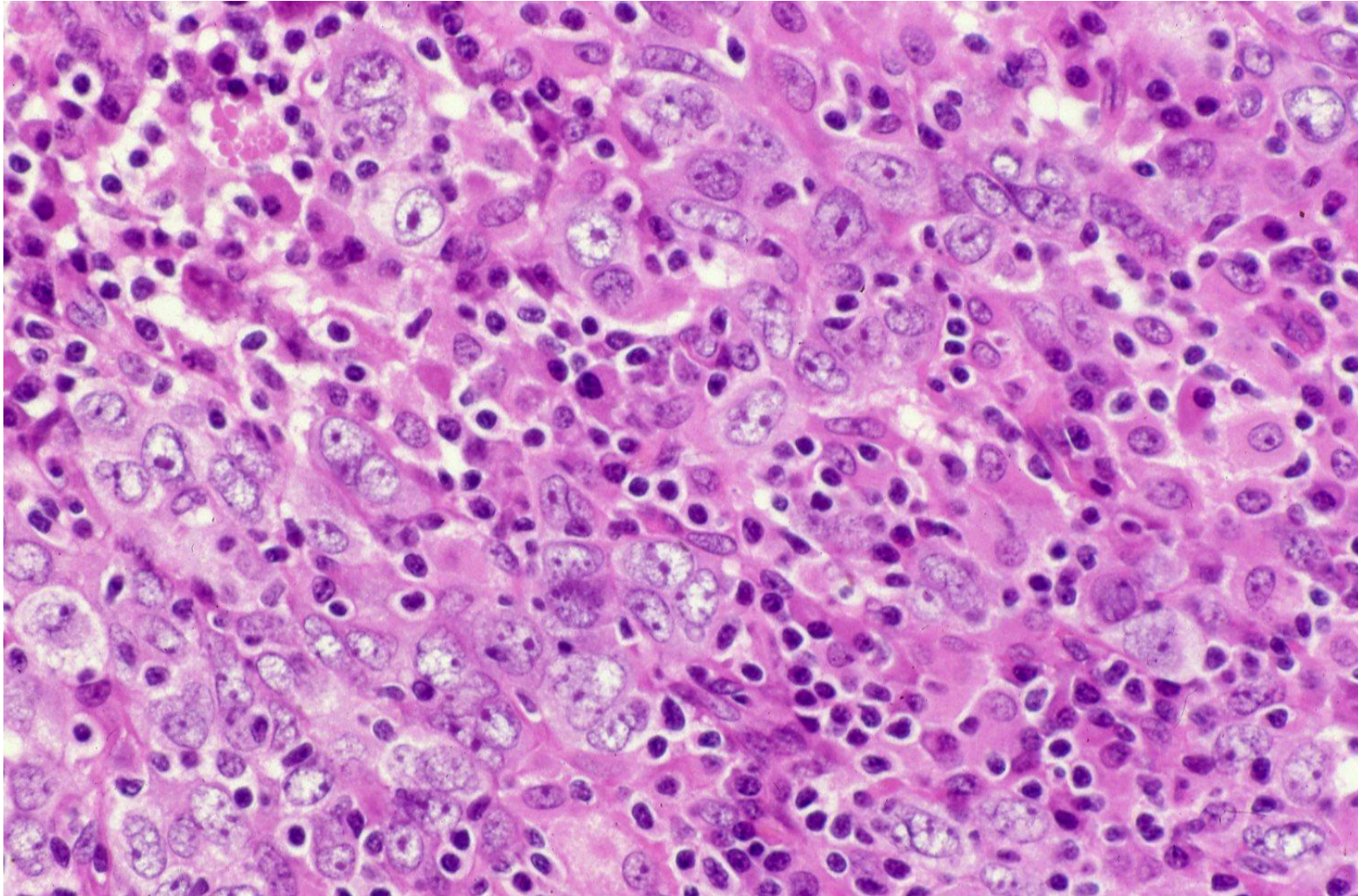
NK/T-cell lymphoma of the nasal cavity is common in Japan. Necrosis is common, and the lymphoma cells express killer cell markers such as TIA-1. left: H&E, right: TIA-1



Pyothorax-related B-cell lymphoma is relatively common in Japan. Old tuberculous pleuritis induces EBV-induced large B-cell lymphoma in the pleural cavity. Left: H&E, right: EBER



Persistent use of low-dose methotrexate for treating rheumatoid arthritis may provoke methotrexate-associated lymphoproliferative disorder. Growth of EBV-infected, CD20-positive lymphocytes is associated with coagulation necrosis. The disorder tends to occur among the Japanese patients. Left: H&E, right: immunostaining for CD20



EBV-related nasopharyngeal carcinoma (lymphoepithelioma) is common among the Chinese, but infrequent among the Japanese. Non-keratinizing poorly differentiated squamous cell carcinoma accompanies small lymphocytes. H&E

Incidence of hematopoietic disorders

Low incidence of thalassemia in Japan

High incidence of subacute necrotizing lymphadenitis (Kikuchi's disease) in Japan

High incidence of T-cell lymphoma, particularly adult T-cell leukemia/lymphoma, in Japan

High incidence of pyothorax-related lymphoma in Japan

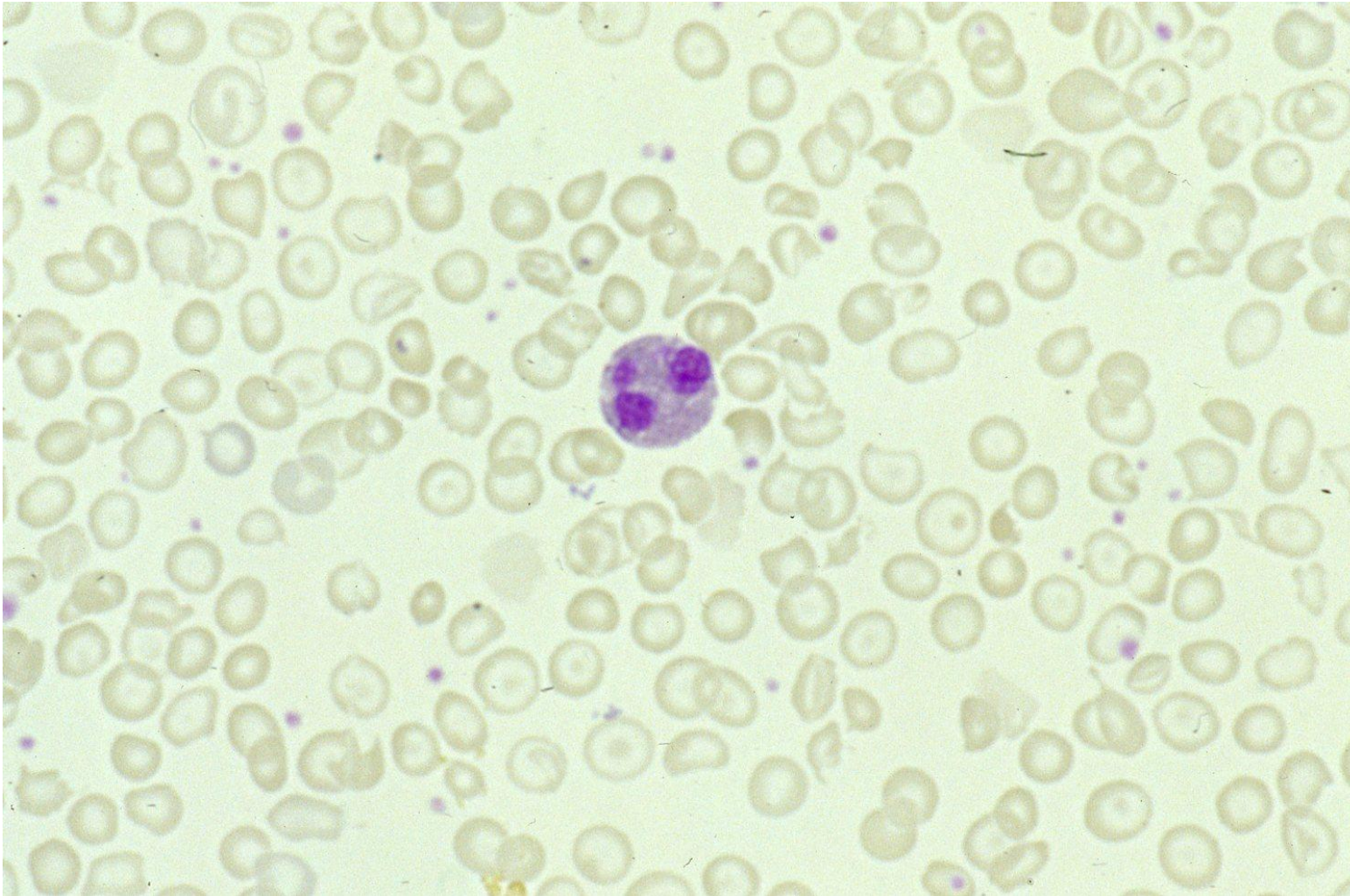
High incidence of NK/T-cell lymphoma of nasal type in Japan

High incidence of chronic myeloid leukemia in Japan

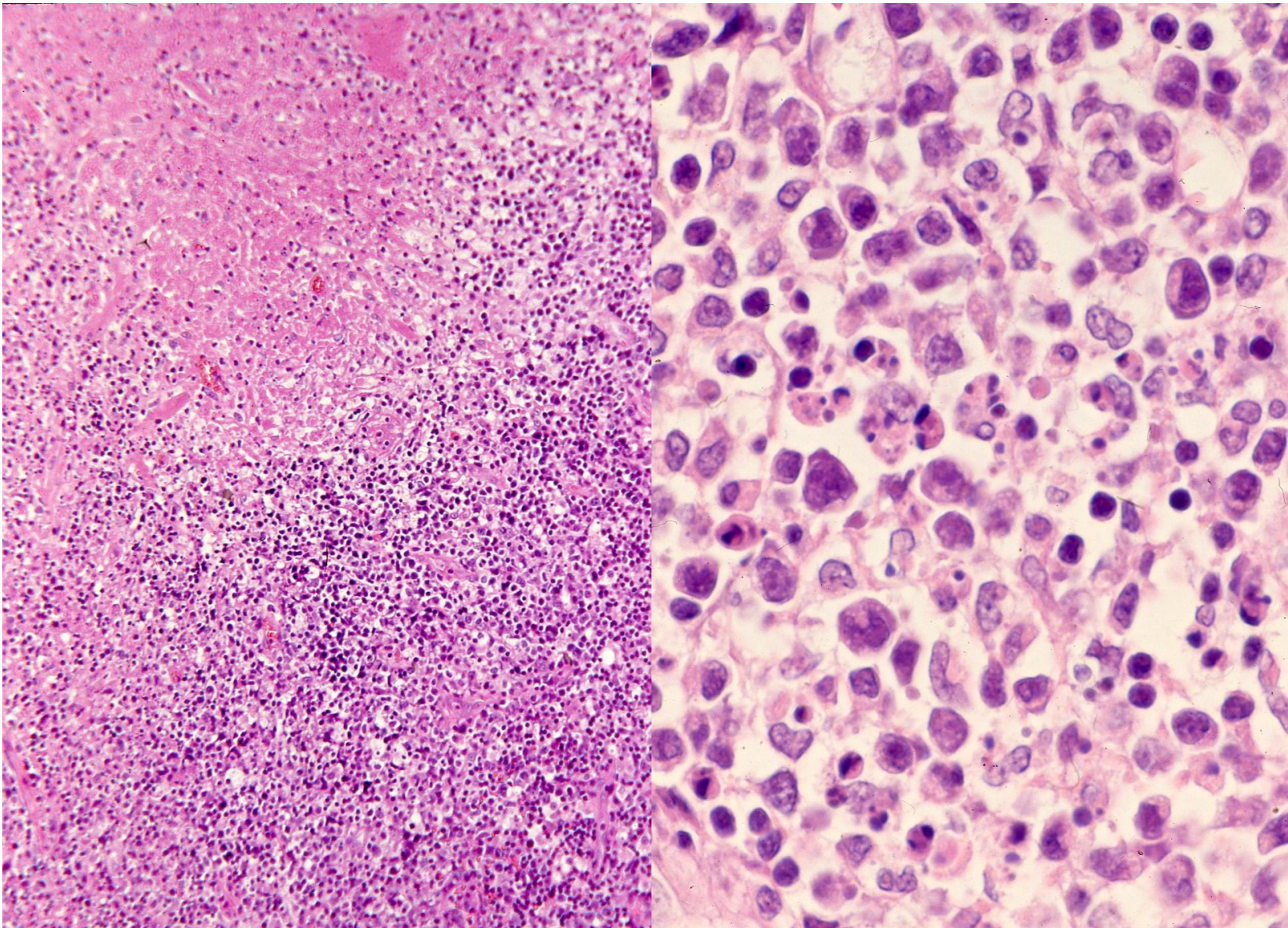
Low incidence of small lymphocytic lymphoma/CLL in Japan

Low incidence of follicular lymphoma in Japan

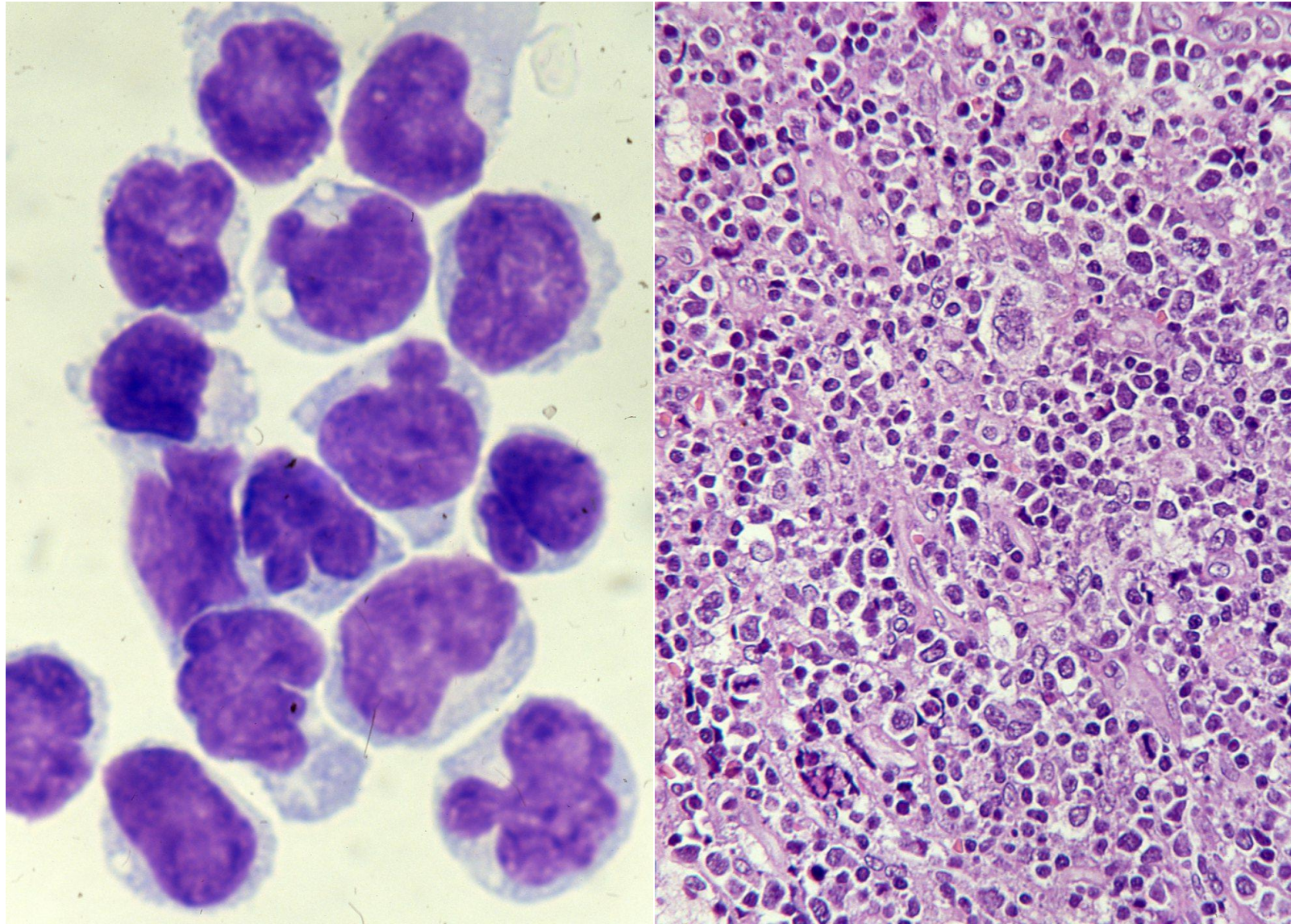
Low incidence of Hodgkin's lymphoma in Japan



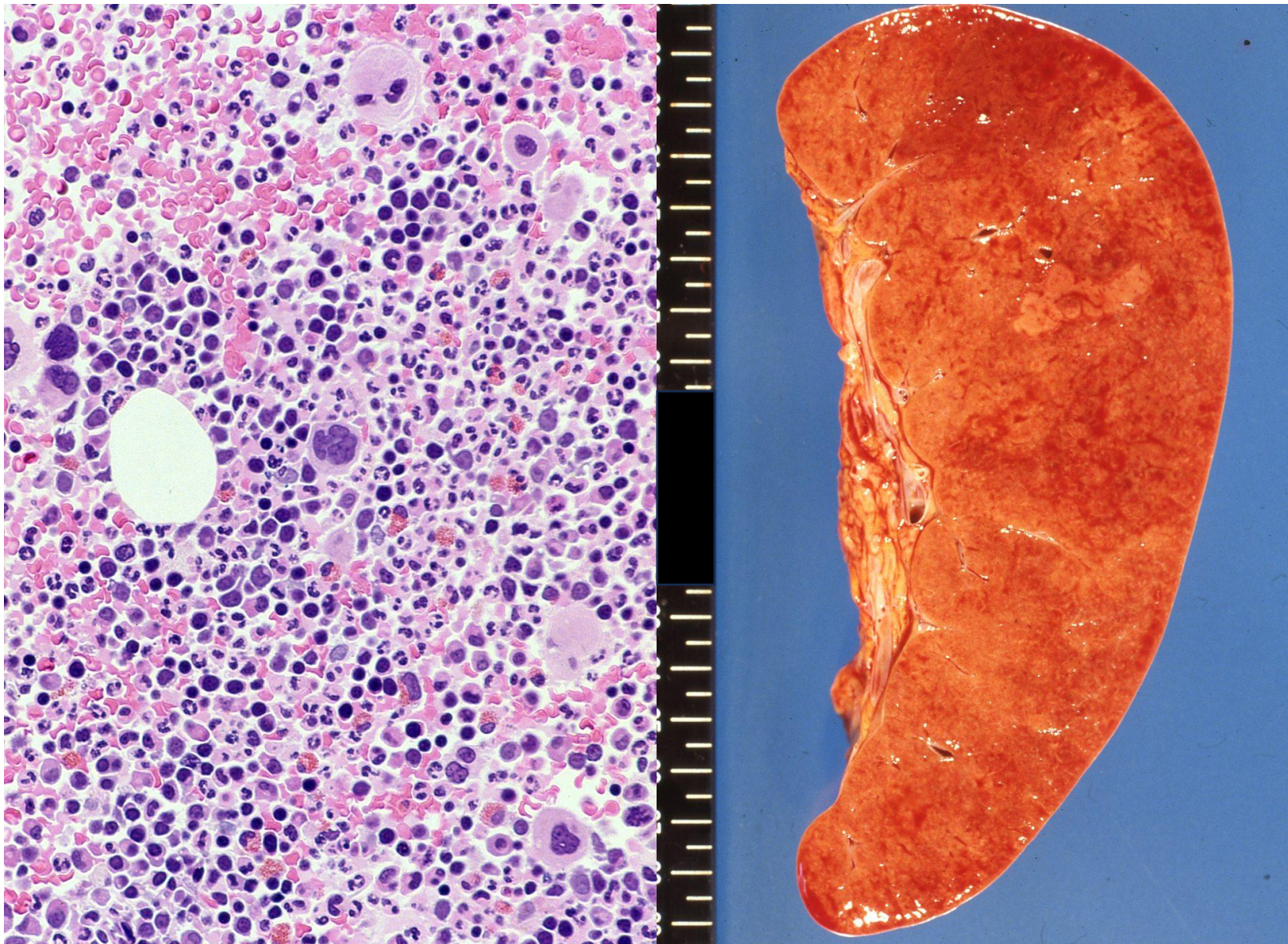
Peripheral blood smear of beta-thalassemia in a Japanese lady. Target appearance is noted in hypochromic erythrocytes. Beta-thalassemia is common among the people in the Mediterranean and Southeast Asian countries, but very rare in Japan. May-Giemsa



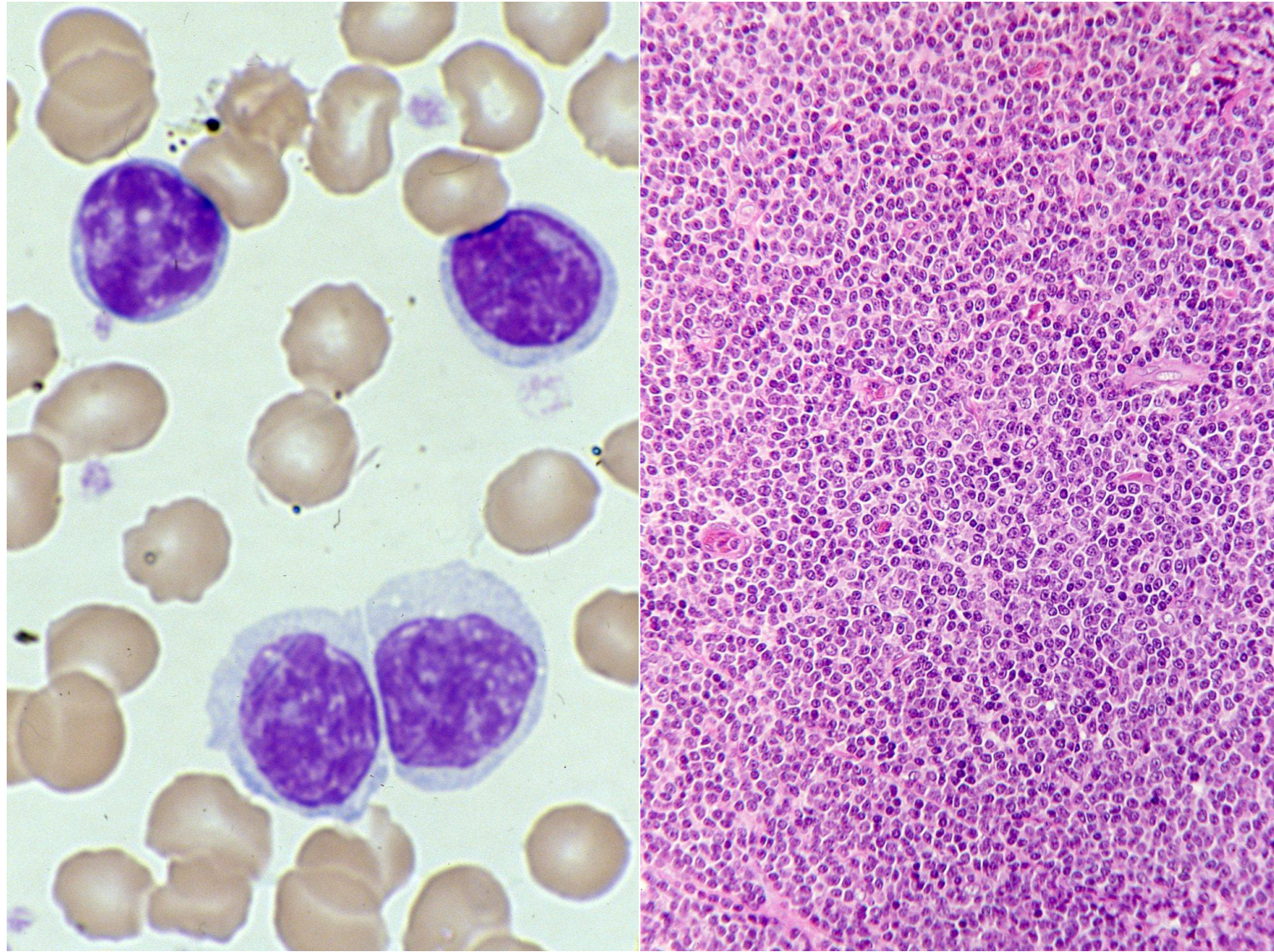
Subacute necrotizing lymphadenopathy (Kikuchi's disease) is common among the Japanese youth. Activated macrophages in the cervical lymph node contain numbers of apoptotic bodies. H&E



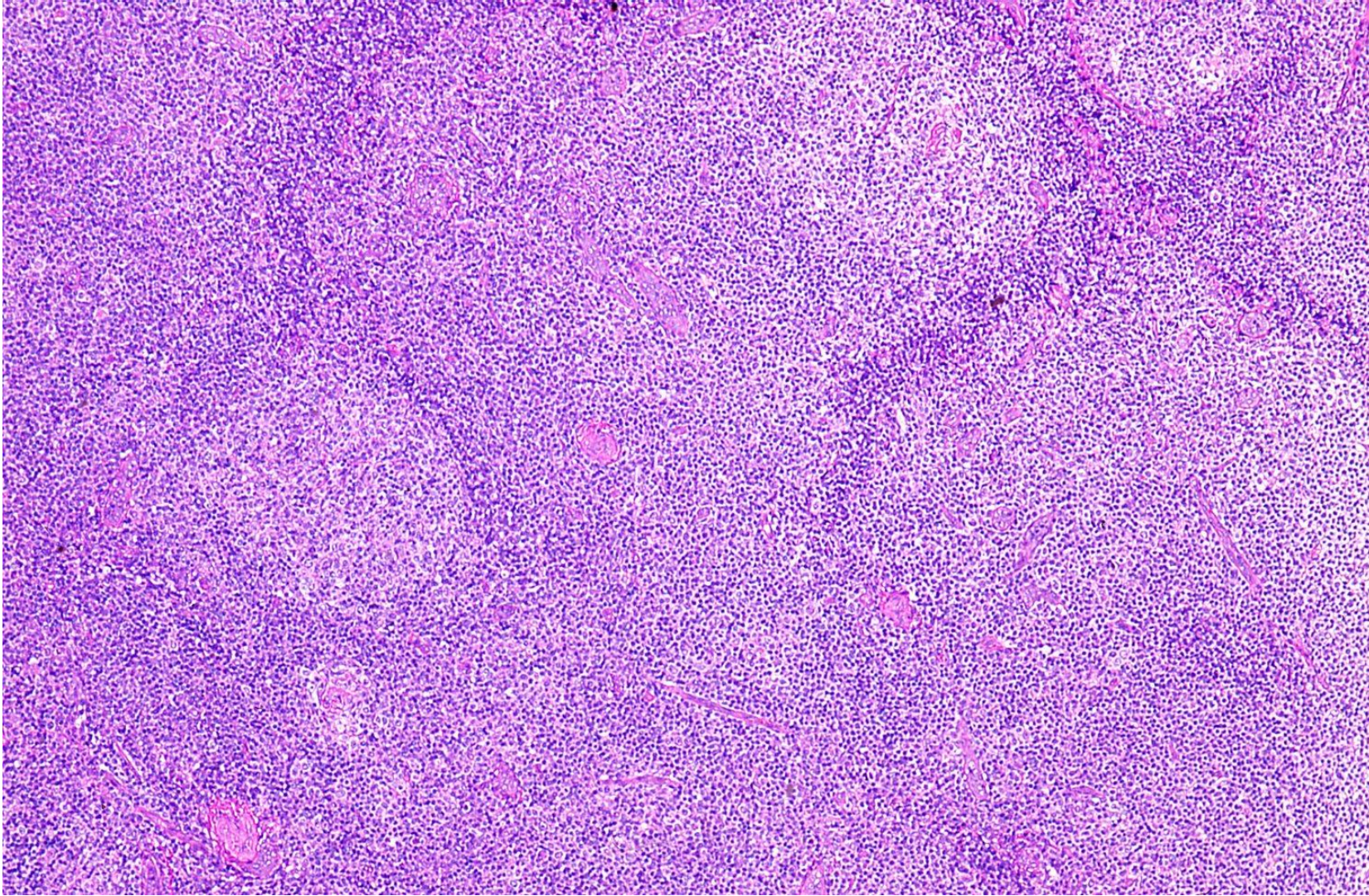
Adult T-cell leukemia/lymphoma caused by transmaternal transmission of HTLV-1 is common in southwestern Japan. Convoluted nuclei are characteristic (left: May-Giemsa). The nodal lesion reveals marked pleomorphism (pleomorphic T-cell lymphoma, right: H&E)



Chronic myeloid leukemia is relatively common in Japan. Among chronic leukemia, the incidence of CML is higher than CLL. Panmyelosis is observed in the bone marrow (left: H&E). Splenomegaly (500 g) is characteristic of CML (right: macro).



Chronic lymphocytic leukemia (left: peripheral blood, May-Giemsa) and small B-lymphocytic lymphoma (right: lymph node biopsy, H&E) are rare in Japan.



Follicular lymphoma is relatively infrequent among the Japanese (H&E).
The most frequent type in Japan is diffuse large B-cell lymphoma.

Vascular diseases

High incidence of Takayasu disease

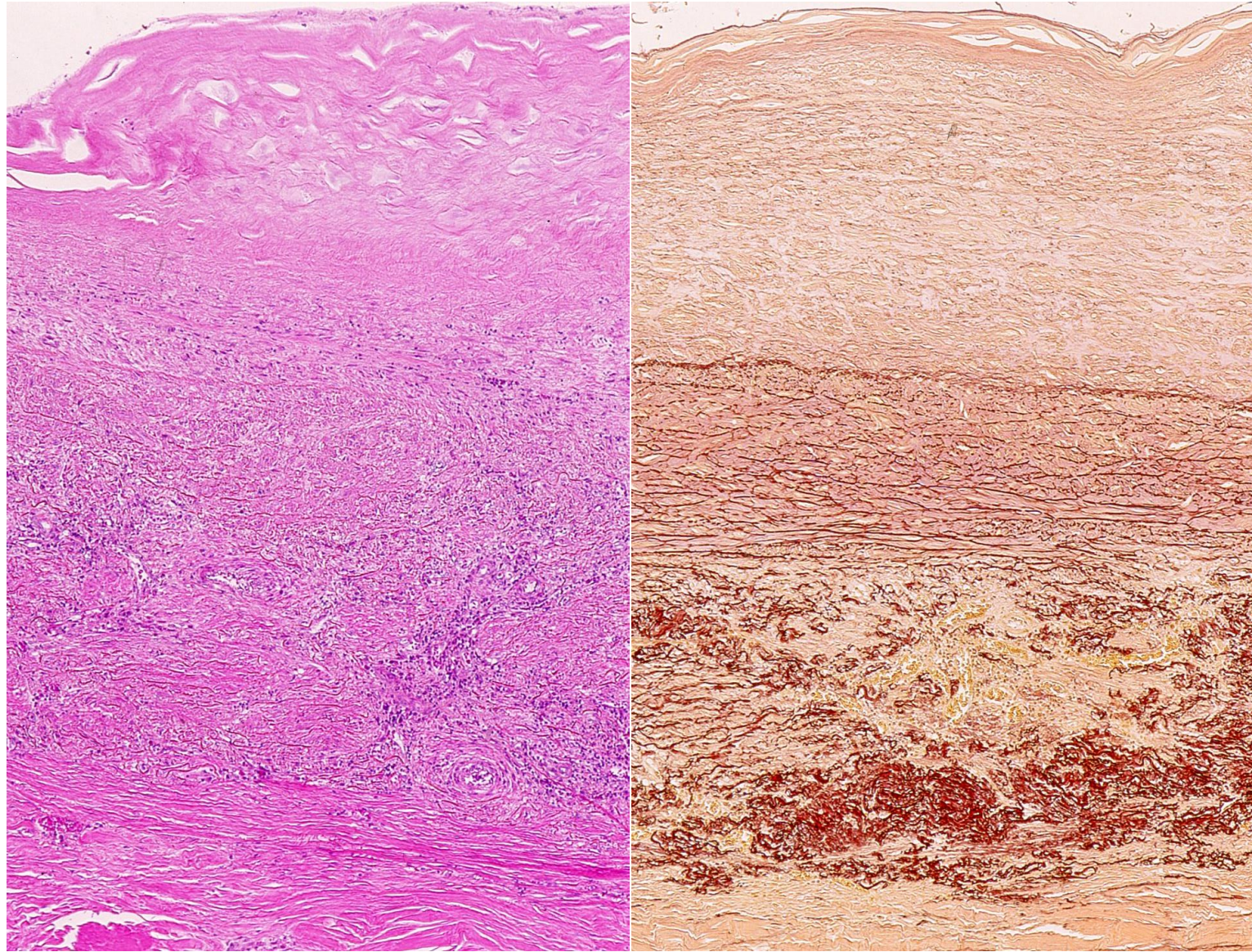
High incidence of Kawasaki disease

High incidence of Behcet disease

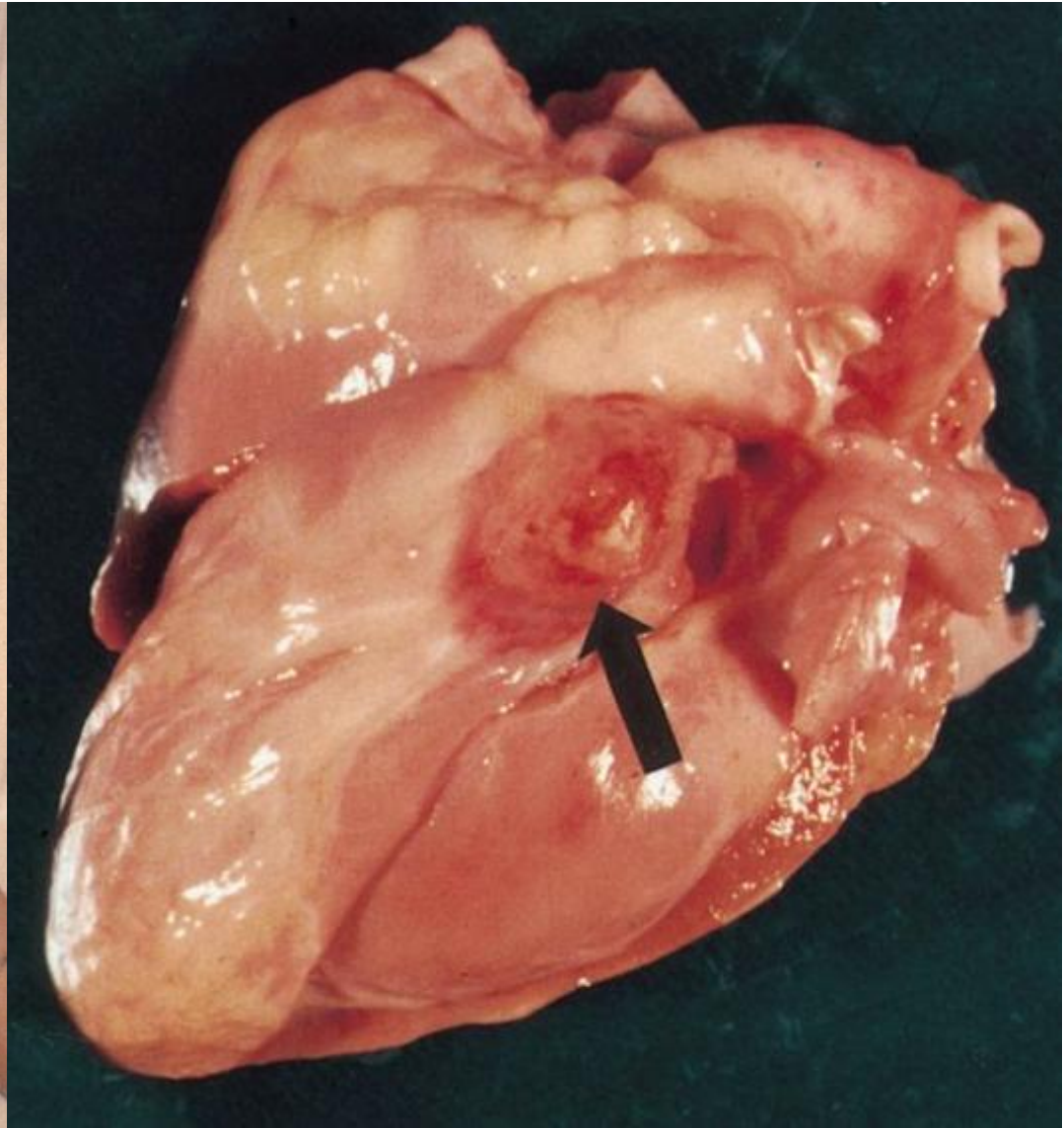
High incidence of Buerger's disease

Low-incidence of temporal arteritis

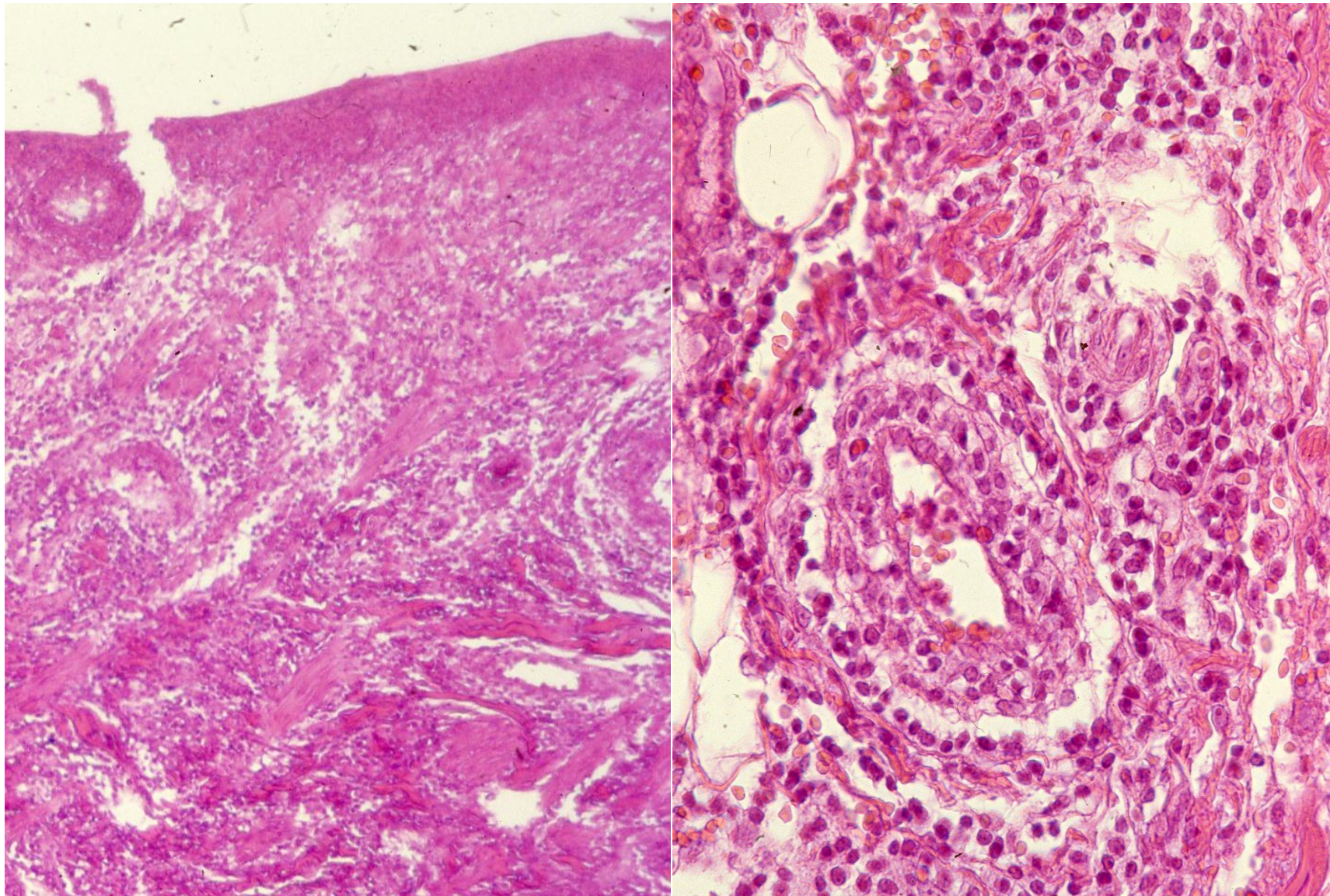
High incidence of Moyamoya disease



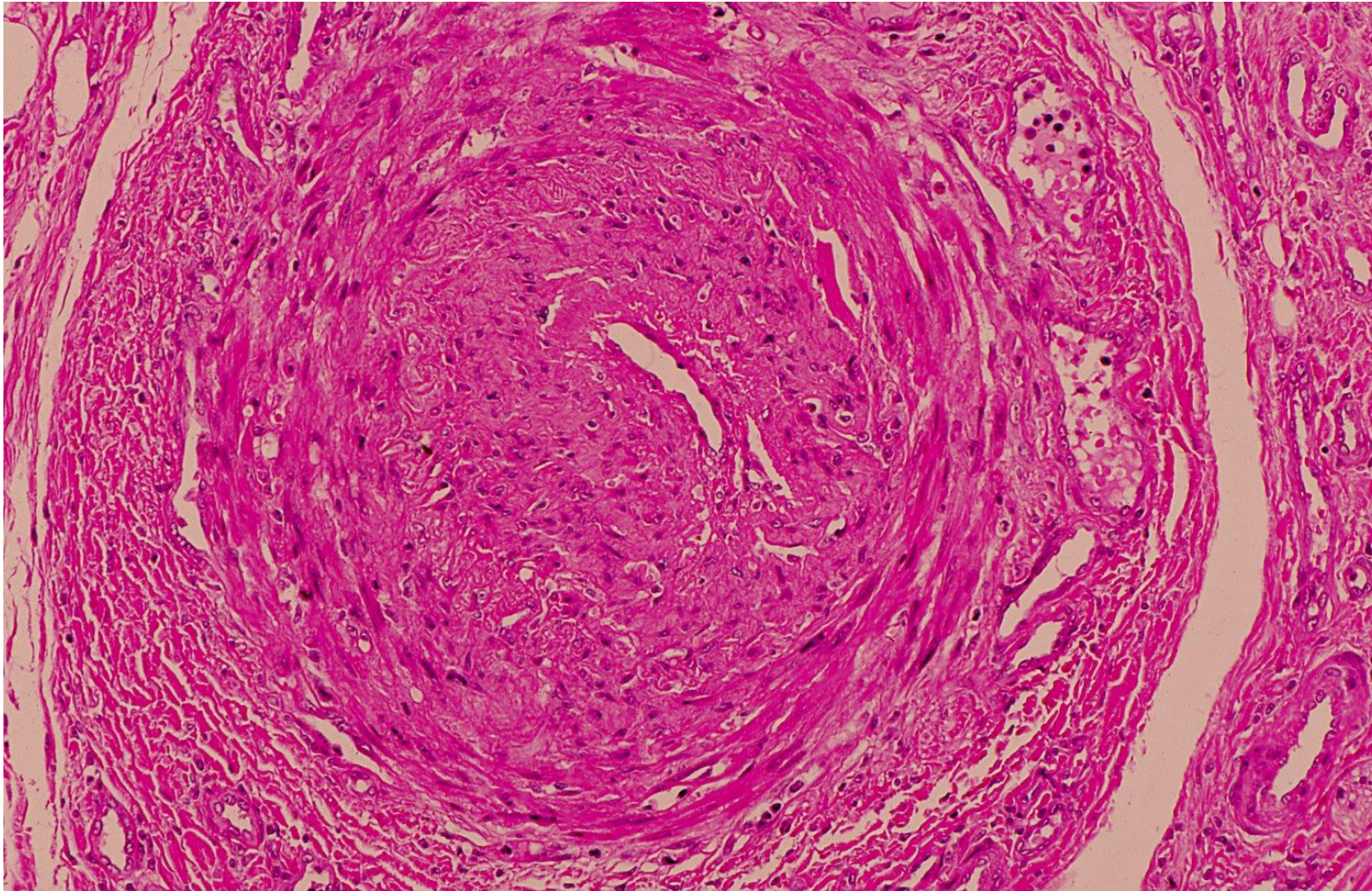
Takayasu aortitis is relatively common among young Japanese women. Adventitial fibrosis with moth-eaten loss of elastic lamina in the outer half of the media is noted. Lymphocytic infiltration is seen around the vasa vasorum. Left: H&E, right: EVG



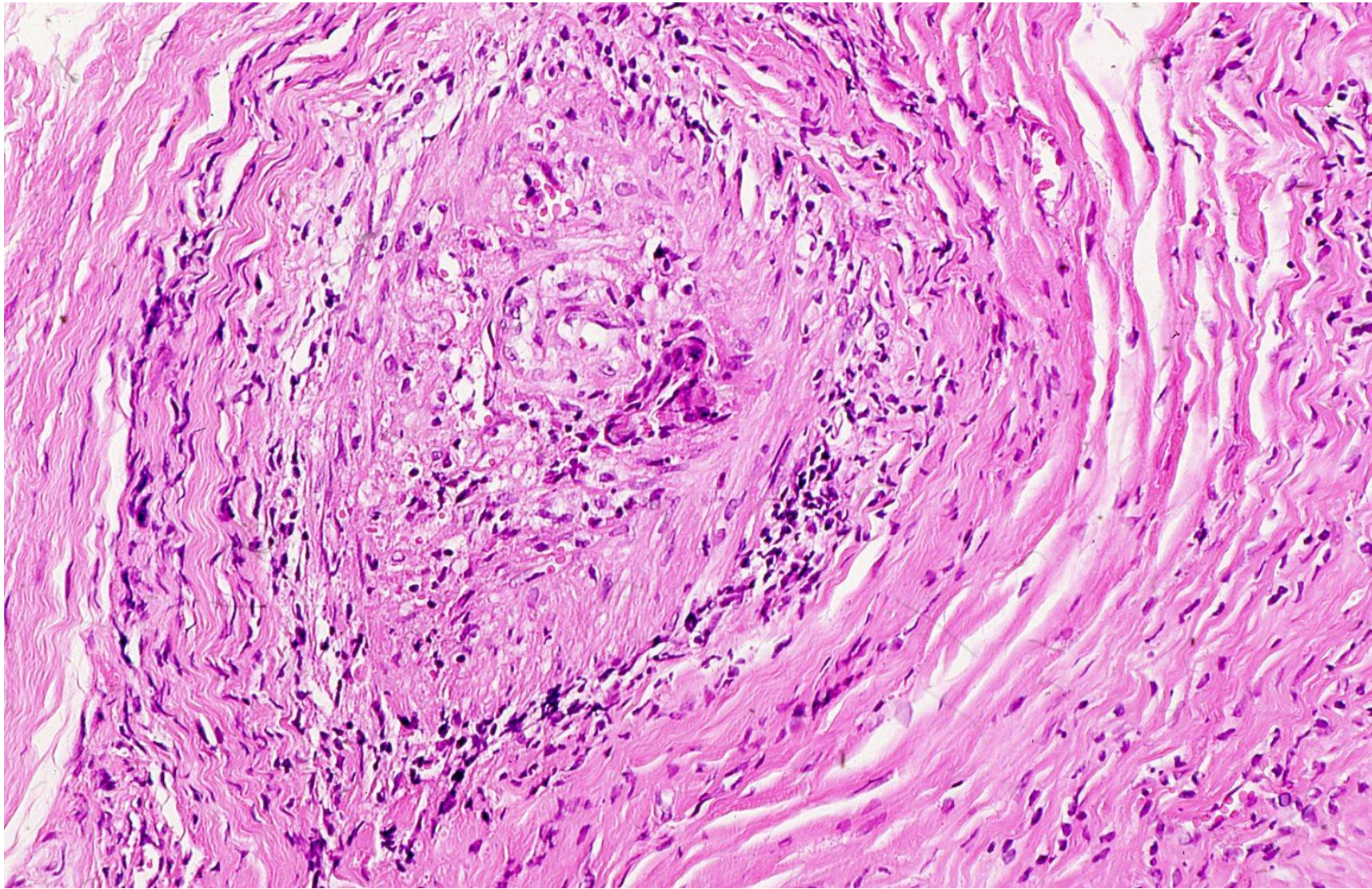
Kawasaki disease is featured by fever and skin rash. Coronary aneurysm (arrow) may cause the death of the affected infant.



Behcet disease (a 50 y-o male patient). Scrotal ulcer microscopically reveals active angiitis in the dermal small artery. H&E



Bürger's disease (thromboangiitis obliterans). Thrombotic obstruction of a small artery of the amputated foot is evident (H&E). The disease is closely related to smoking. Recently, the incidence of Bürger's disease has significantly been decreased in Japan.



Temporal arteritis (giant cell arteritis) is infrequently seen among the Japanese aged. The arterial lumen is occluded by the inflammatory process. H&E



The terminal portion of the internal carotid artery

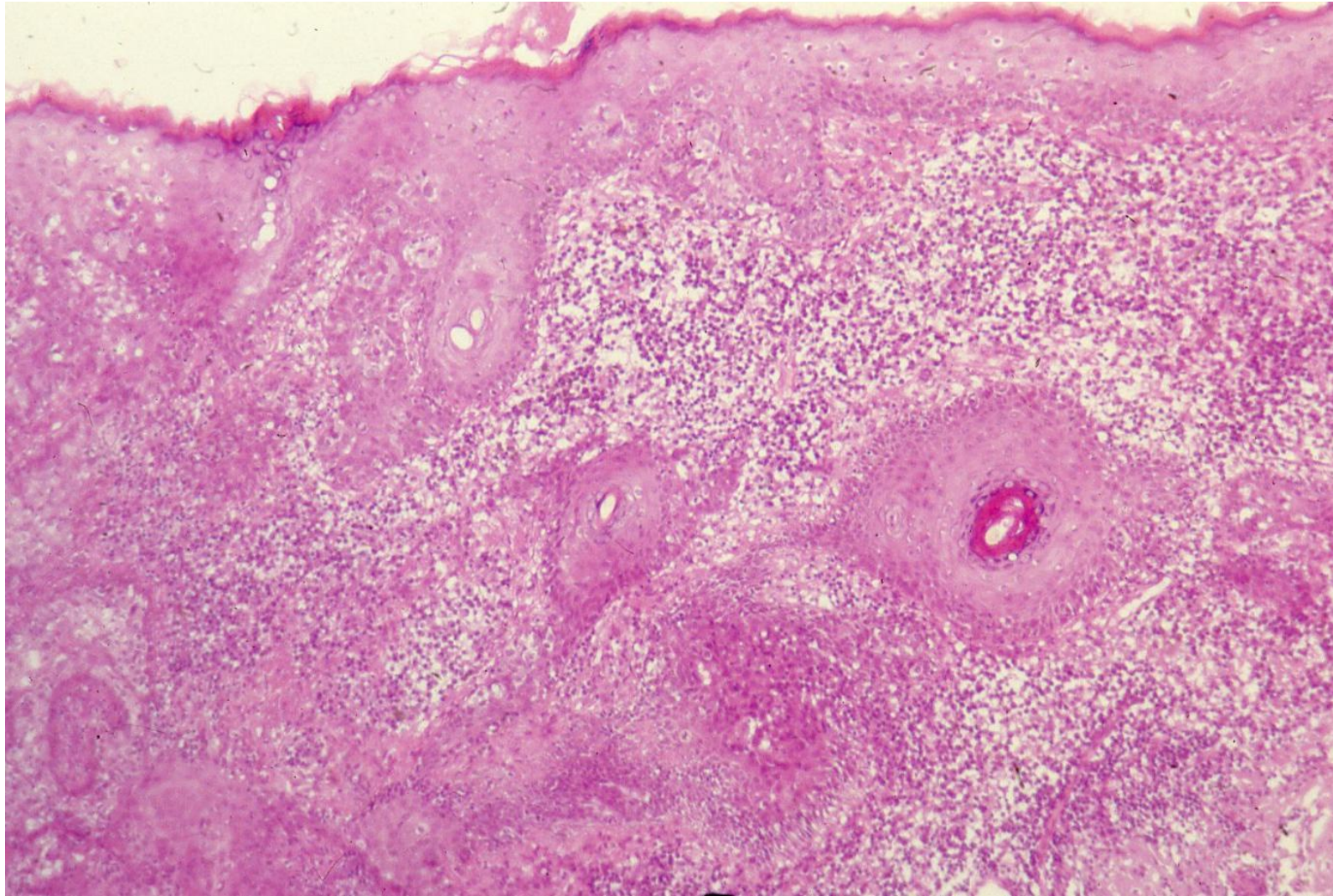


The anterior cerebral artery

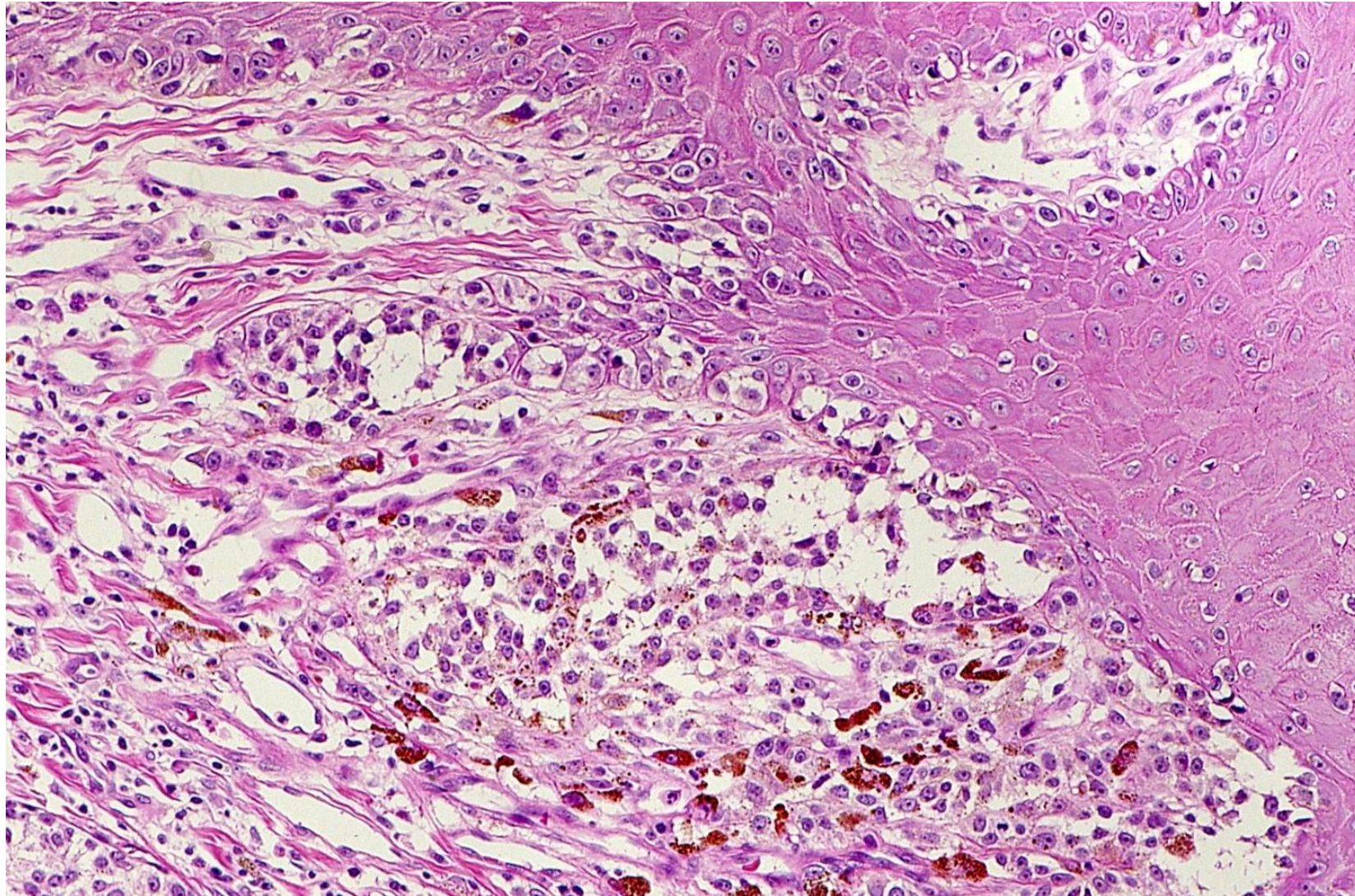
Moyamoya disease (occlusion in the circle of Willis). Gradual obstruction of the terminal portion of the internal carotid artery caused collateral fine Moyomoya (misty or foggy) arterial vessels are formed in the base of the brain. Cerebral infarction or subarachnoid hemorrhage follows. The disease is relatively common in Japan. The lumina of arteries of the circle of Willis are completely occluded. Elastica-HE

Skin lesions

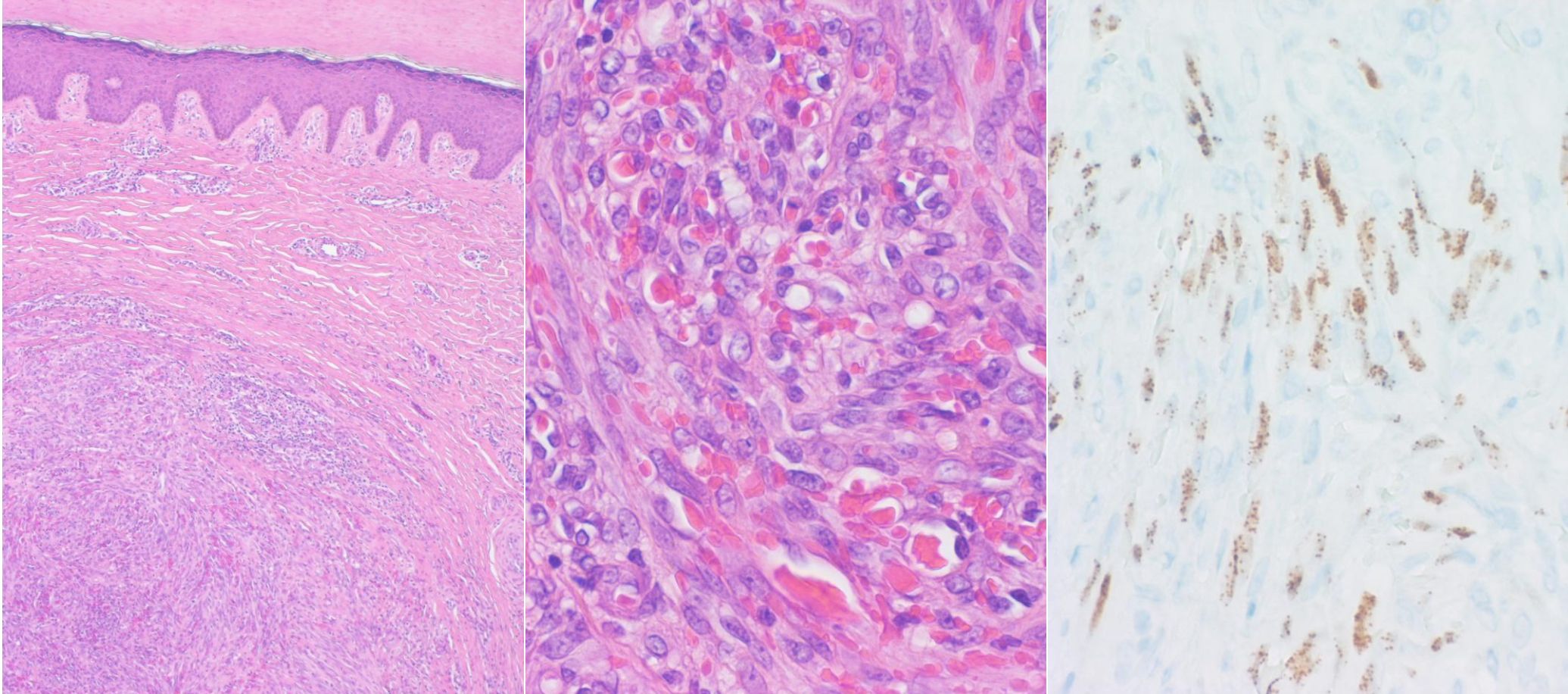
- 1) Low incidence of actinic keratosis and squamous cell carcinoma of the skin in Japan
- 2) Low incidence of malignant melanoma in Japan
- 3) Low incidence of Kaposi's sarcoma in Japan
- 4) High incidence of Kimura's disease in Japan
- 5) High incidence of atopic dermatitis in Japan
- 6) High incidence of Mongolian spots



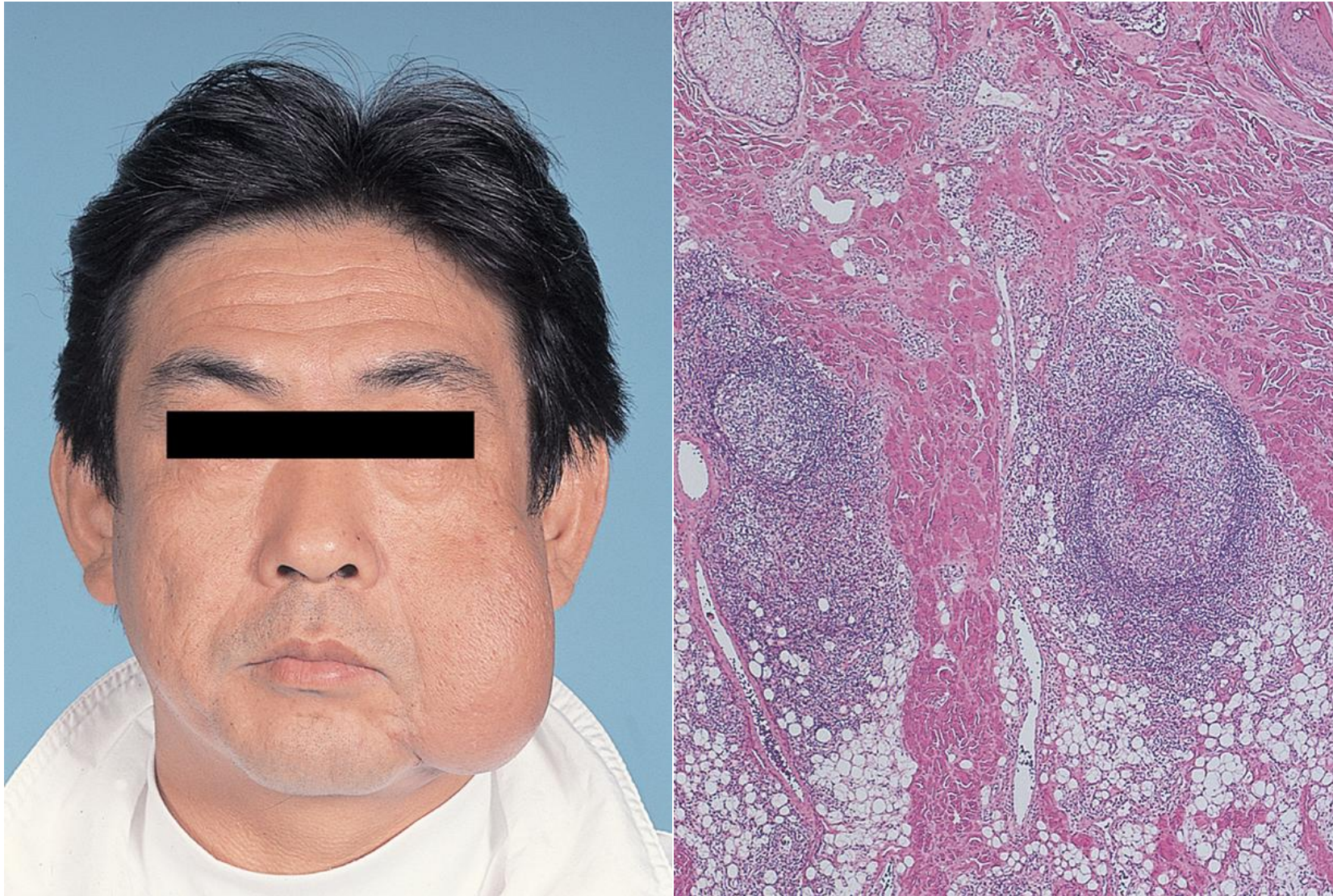
Squamous cell carcinoma of the facial skin of the aged, arising from actinic keratosis (H&E). Invasive squamous cell carcinoma occurred in the background of solar keratosis. The parabasal layer of the overlying epidermis is thickened. The ultraviolet-activated lesion of this type is relatively infrequent in Japan.



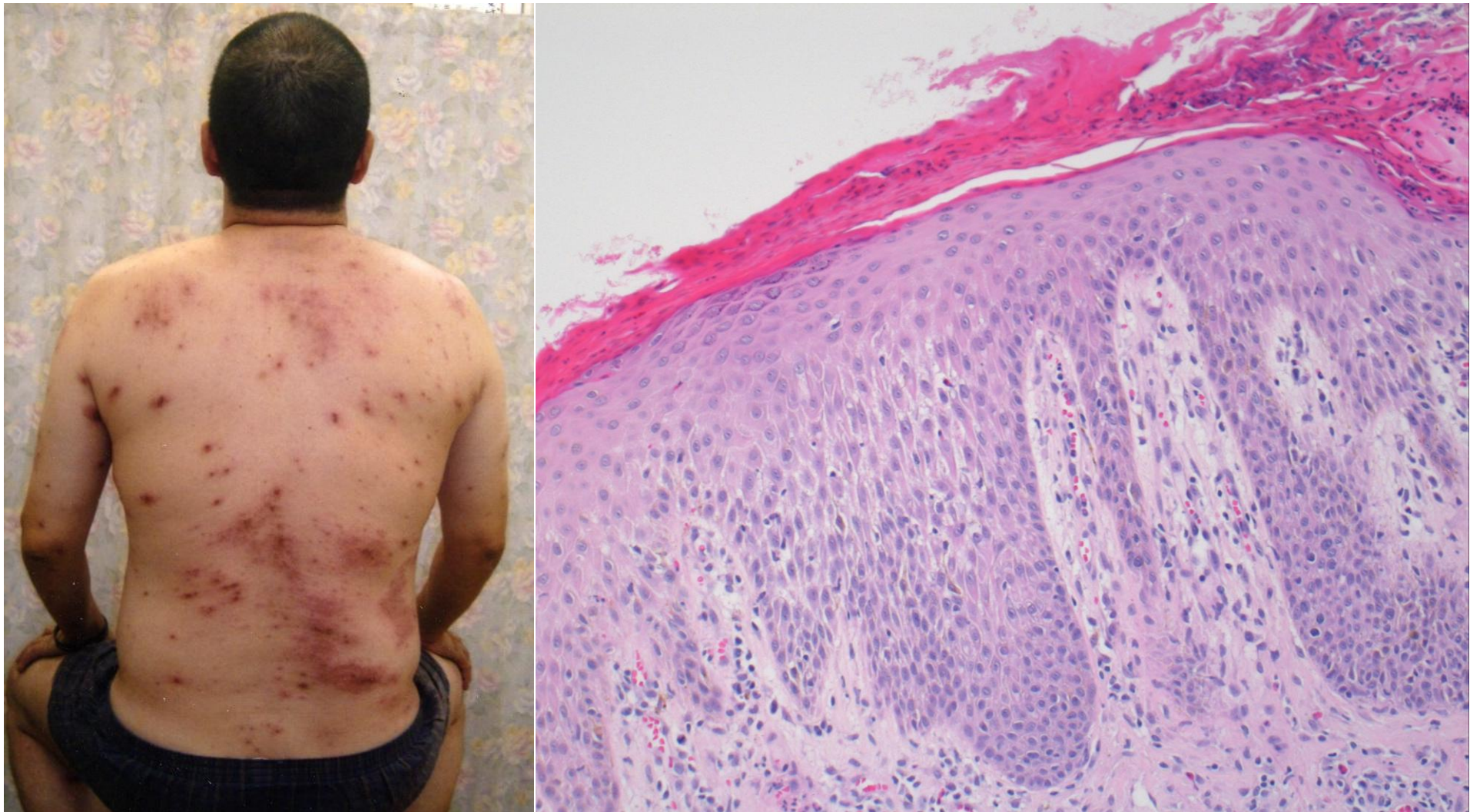
Malignant melanoma of the toe. Melanin-producing atypical nevoid cells invade the dermis. The melanoma cells with clear cytoplasm are also distributed in the basal and parabasal layer. H&E



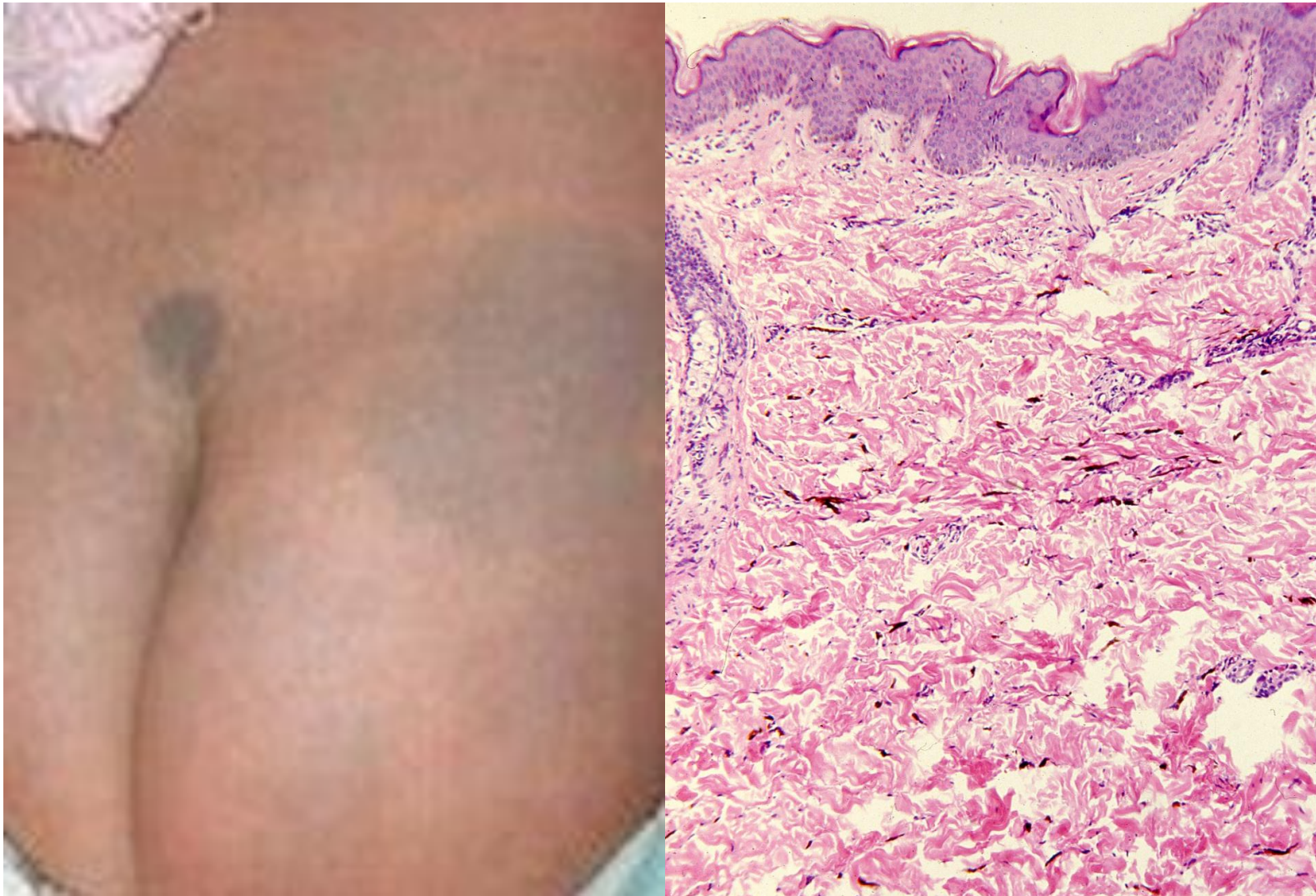
Kaposi's sarcoma of the foot of an HIV-positive 49 y-o male patient. A deep dermal nodule consists of spindle cells forming vascular lumina (left & center: H&E). The nuclei are immunoreactive for HHV8 antigen. The low incidence of Kaposi's sarcoma in Japan is related to the low prevalence of AIDS.



Kimura's disease in a 35 y-o male patient. A large subcutaneous tumor in the cheek microscopically reveals lymphoid hyperplasia with marked eosinophilia. WBC 8,200/ μ L with 25% eosinophils. Left: macro, right: H&E



Atopic dermatitis in a 50- y-o male patient. He had 10-month history of chronic prurigo treated with steroid ointment. Biopsy reveals acanthosis, spongiosis and parakeratotic hyperkeratosis. Left: macro, right: H&E



Mongolian spots on the hip of a 10 y-o girl. Biopsy was taken from the bluish-colored skin. Spindle-shaped bland melanocytes are ectopically clustered in the upper dermis (left: H&E).

Disorders of the other systems

High incidence of pollen allergy (Japanese cedar tree) in Japan

High incidence of IgA nephropathy in Japan

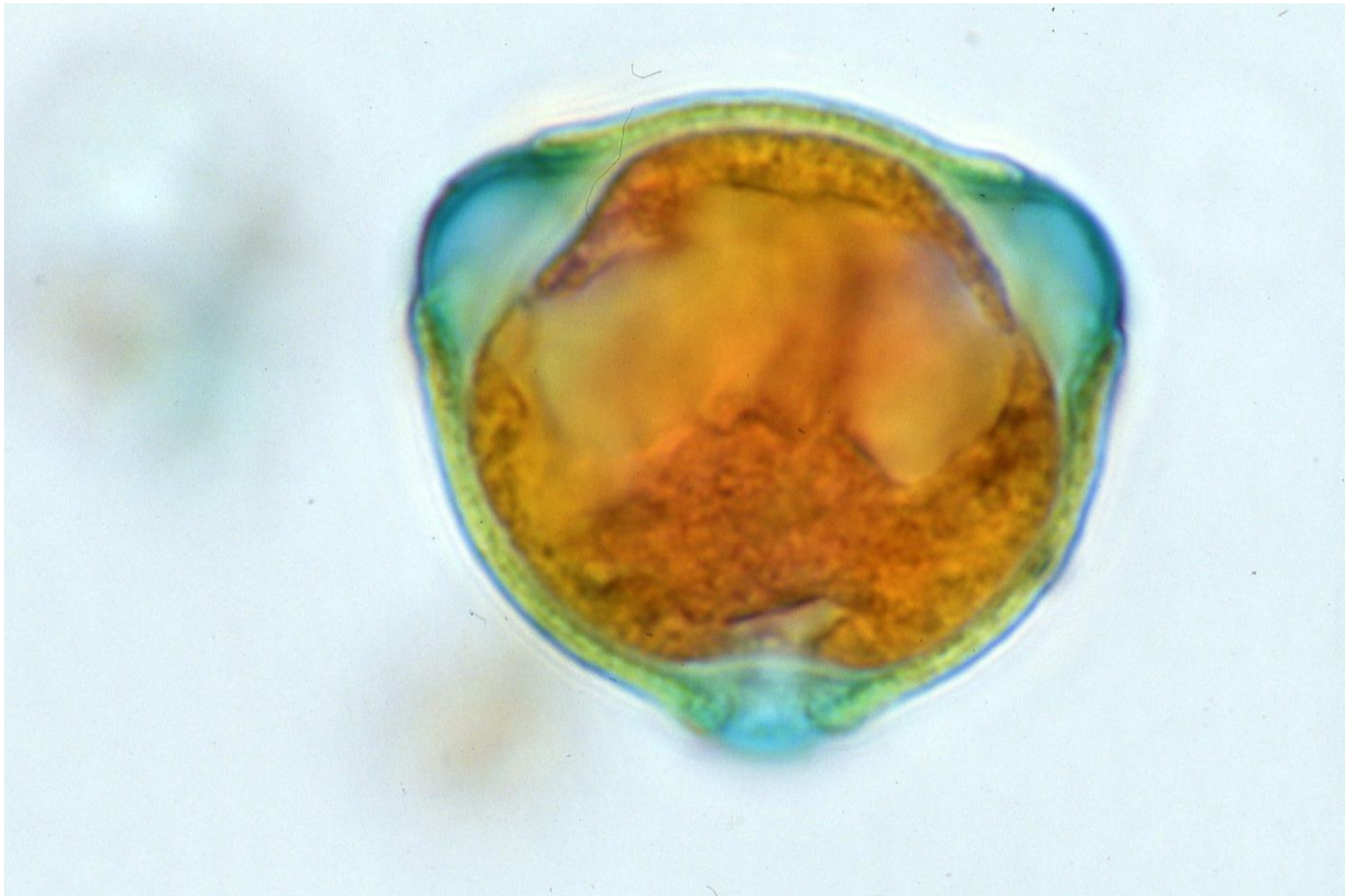
Low incidence of multiple sclerosis in Japan

High incidence of Reye syndrome in Japan

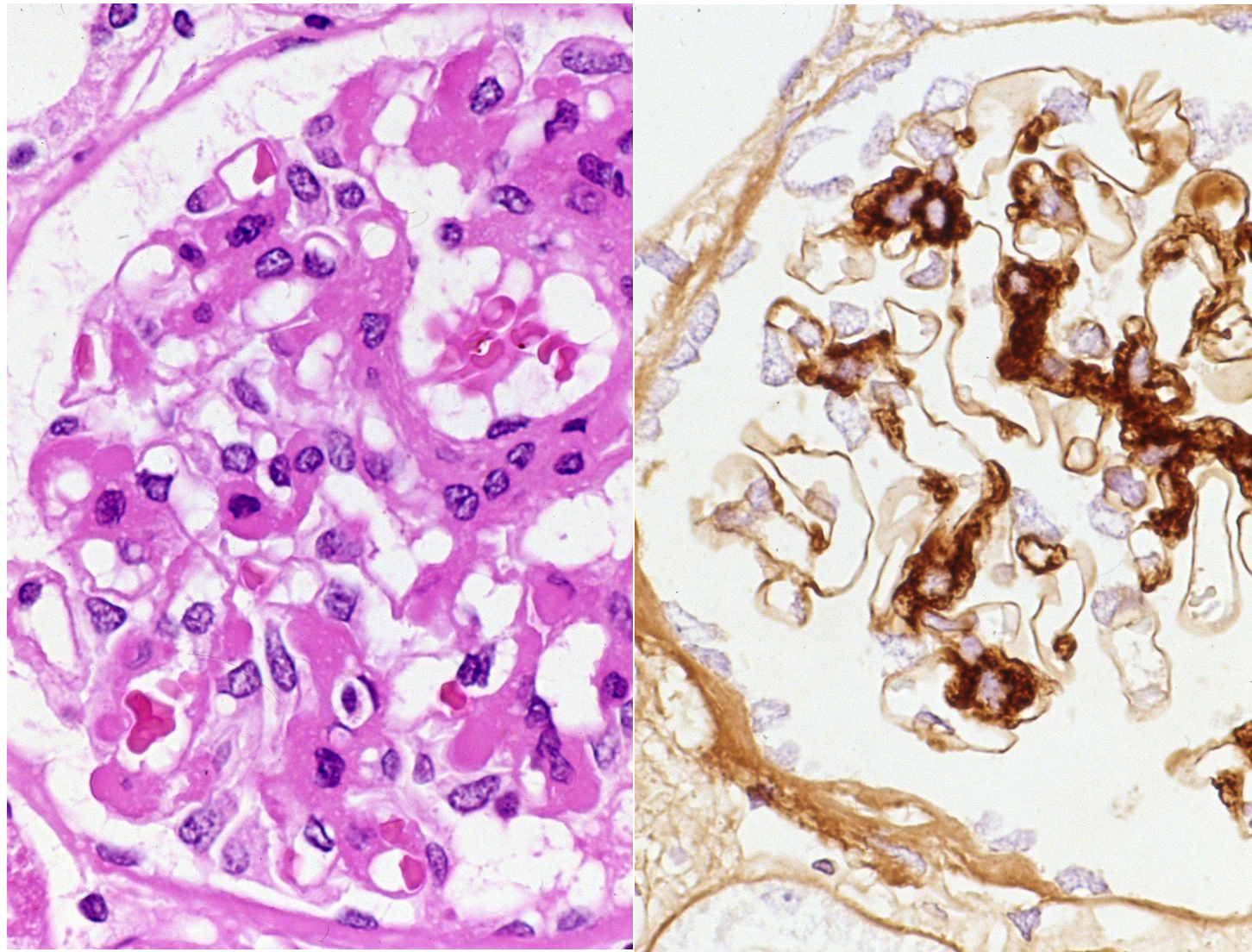
High incidence of HTLV-1-associated myelopathy (HAM) in Japan

High incidence of ossification of the yellow ligament in Japan

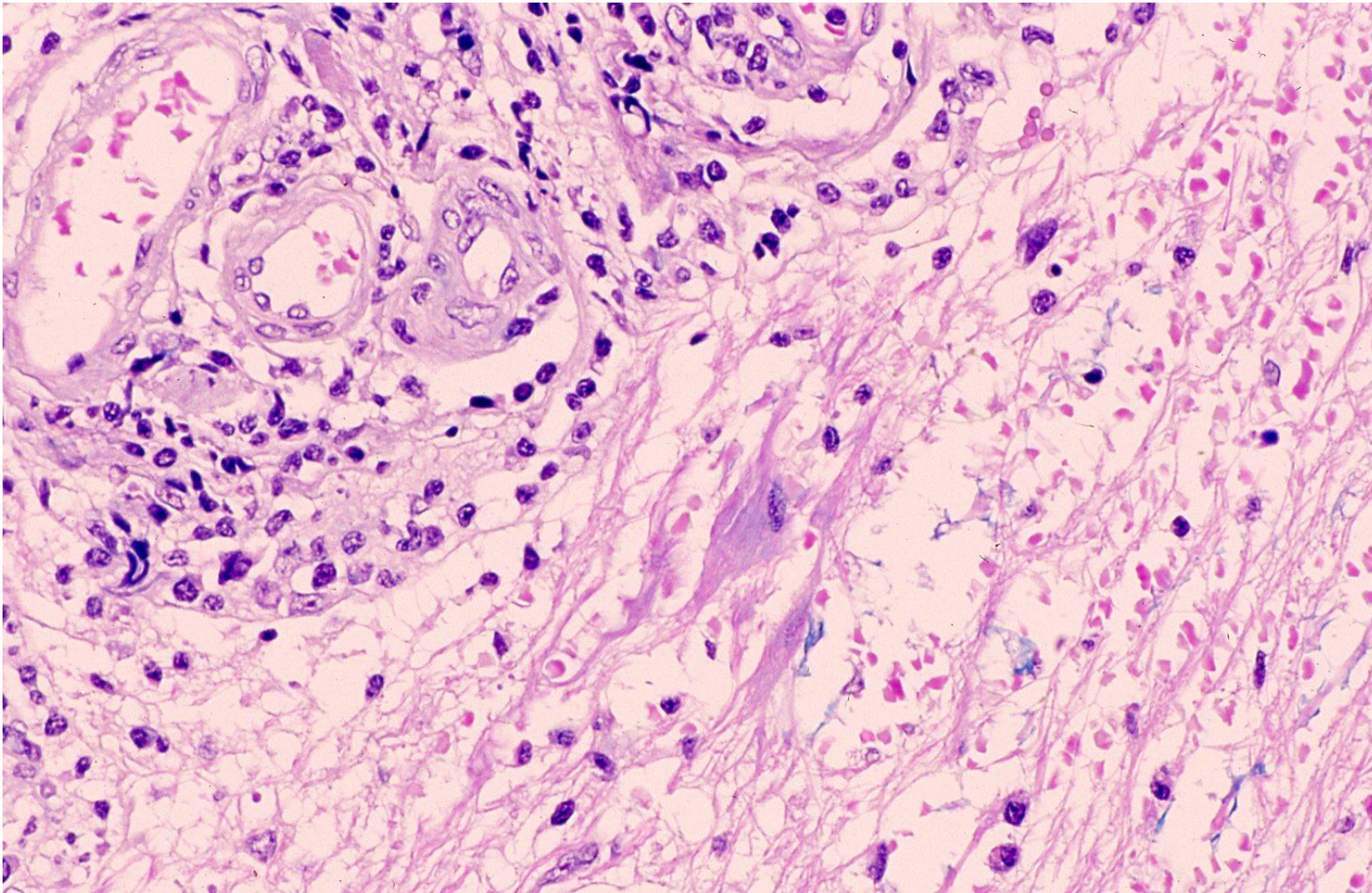
Low incidence of Paget's disease of the bone in Japan



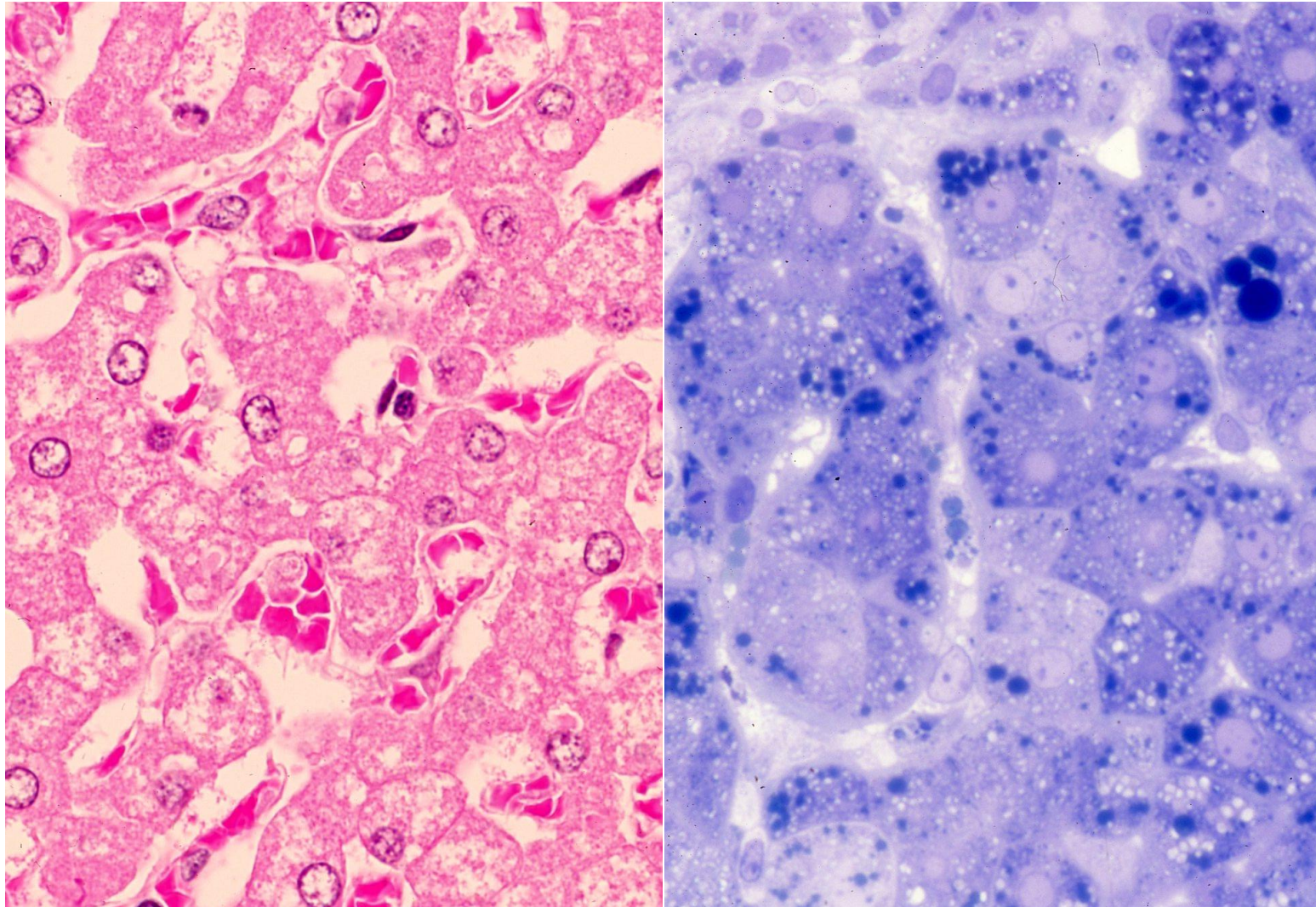
Pap-stained Japanese Cedar tree. The intine is beautifully stained orange, while the exine is stained green. Allergy to the pollen of the Japanese Cedar tree is widespread throughout Japan in the spring season. Since the Japanese Cedar tree is a plant unique in Japan, the allergic disorder to this specific plant pollens is exceptionally seen in Japan.



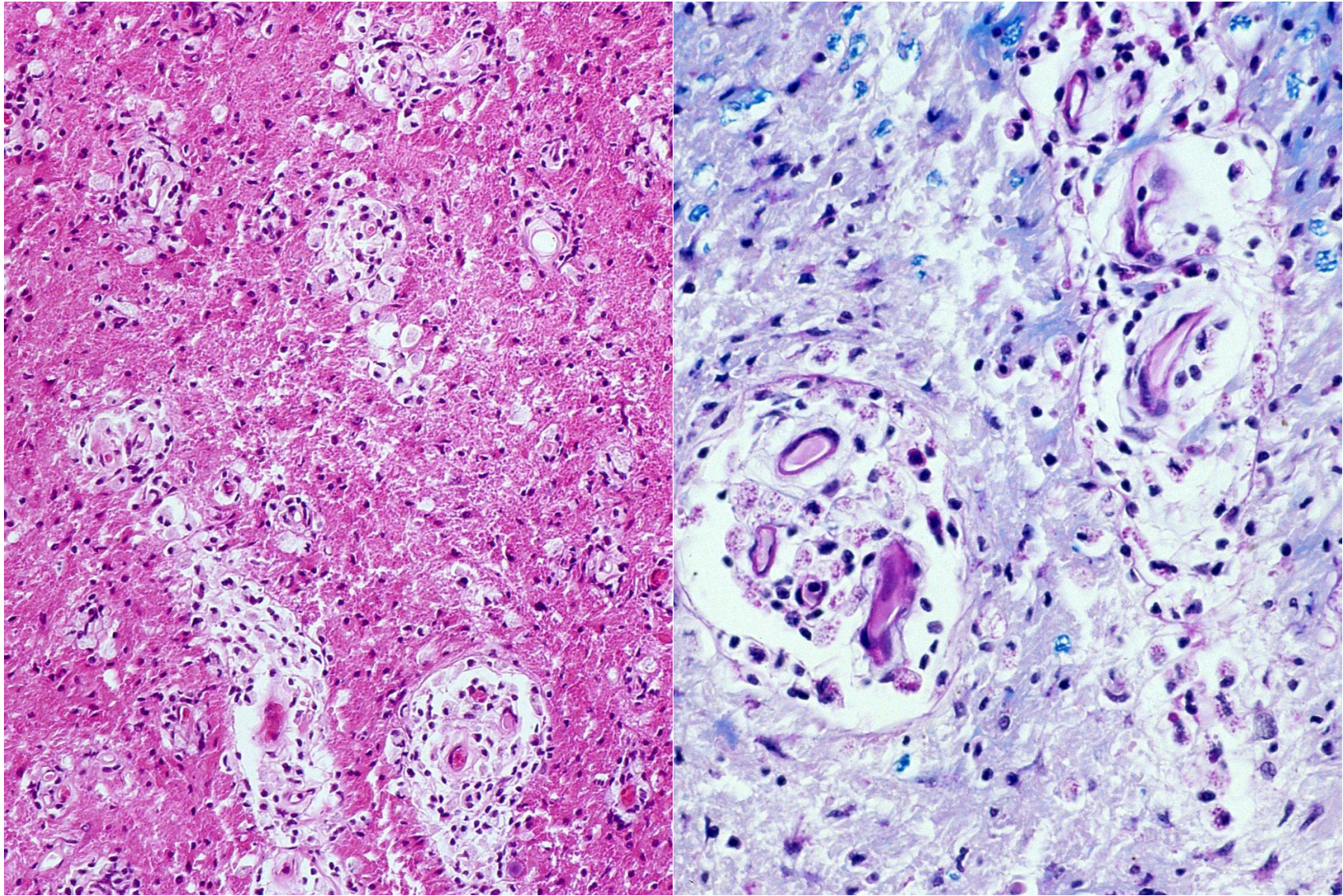
IgA nephropathy in a 38 y-o male patient. IgA deposition is seen in the mesangial matrix. The formation of paramesangial deposits is characteristic. IgA nephropathy is the most common type of glomerulonephritis in Japan. Left: H&E, right: IgA immunostaining



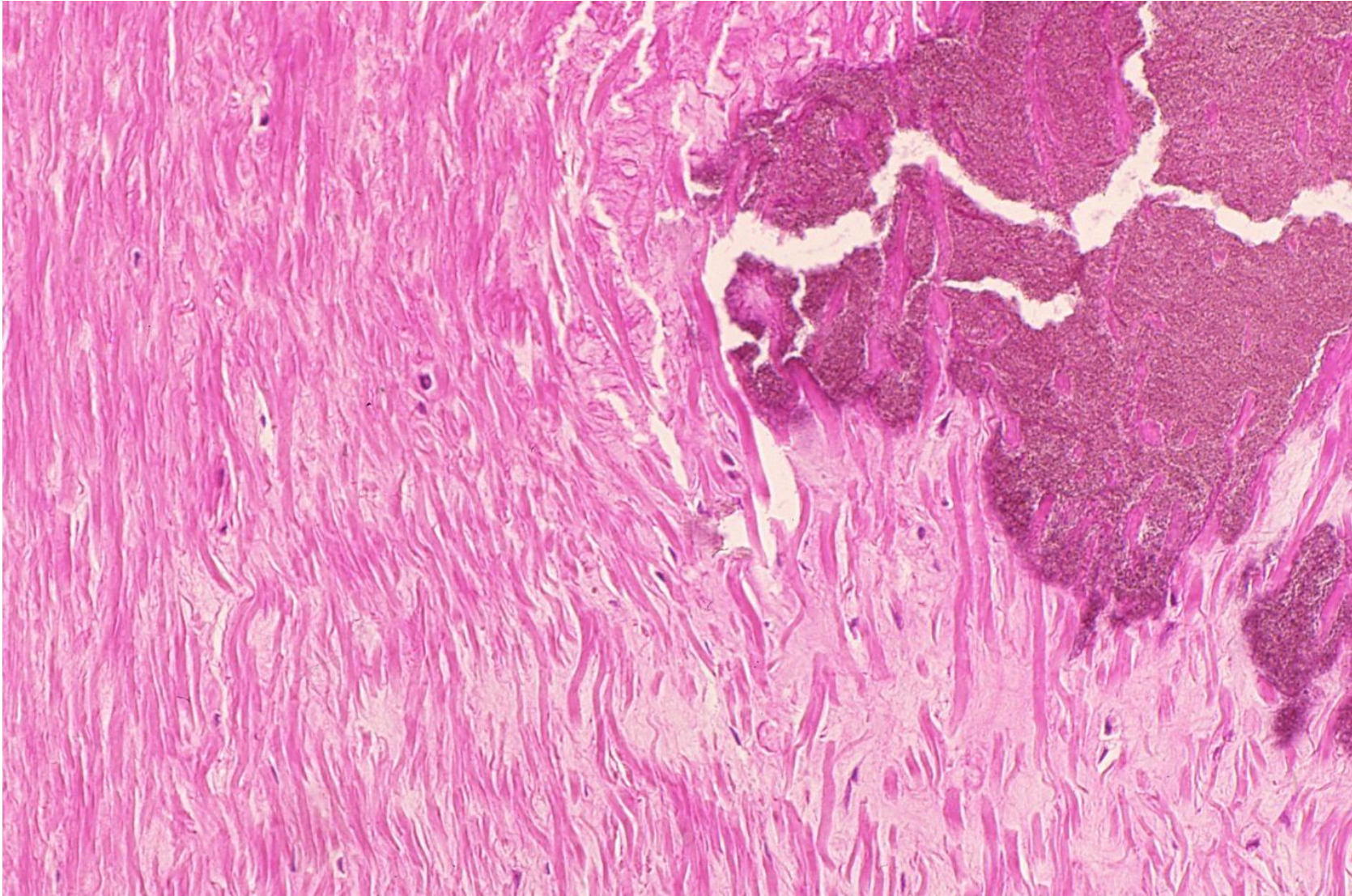
Multiple sclerosis seen in the spinal cord of a 45 y-o female patient. Perivascular infiltration of lymphocytes and macrophages is observed. The incidence of multiple sclerosis is very low in Japan. H&E



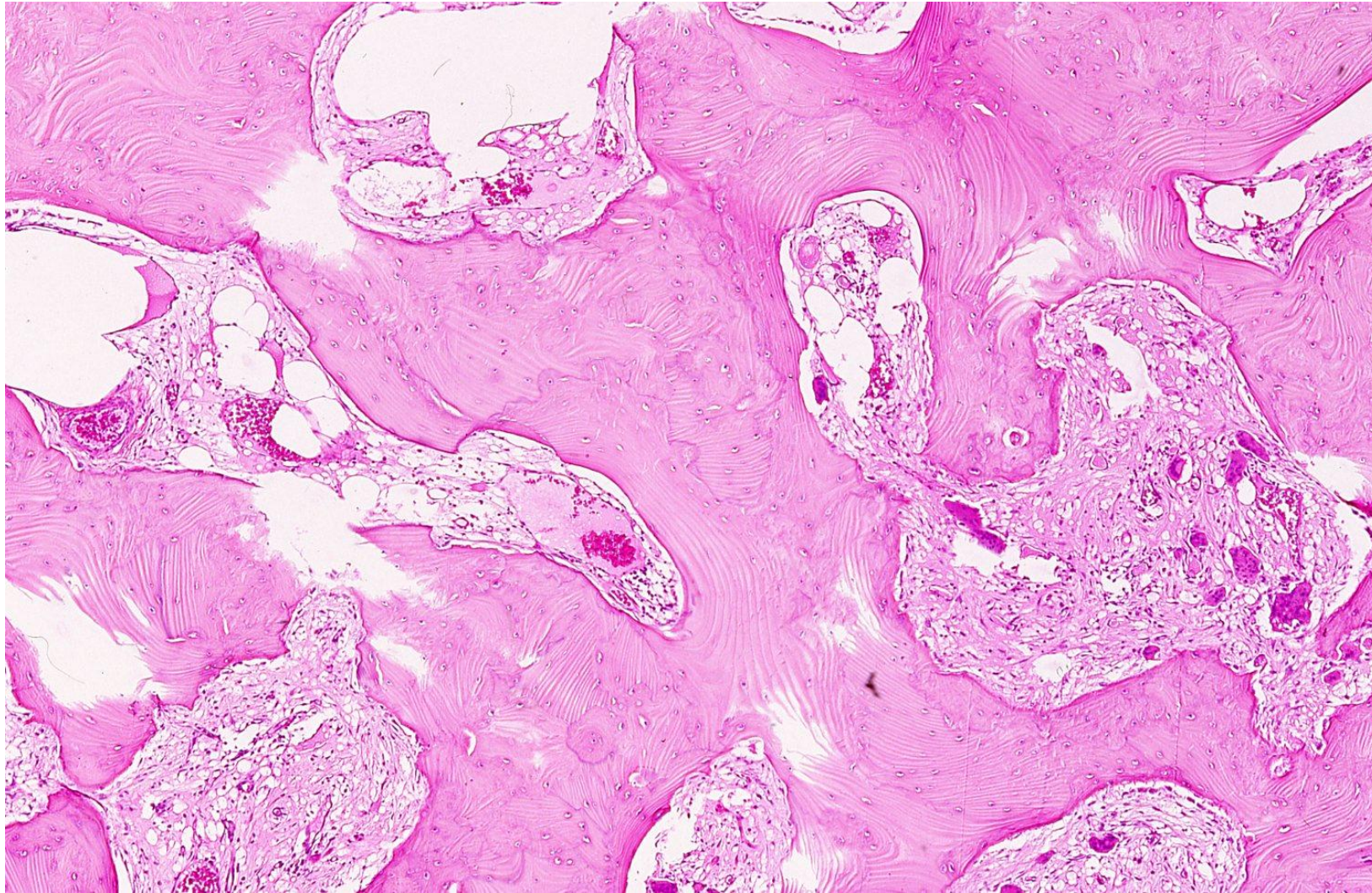
Reye syndrome is an acute encephalopathy of children after taking aspirin against febrile viral infection. The liver shows fatty change of fine droplet type, caused by the mitochondrial injury (left: H&E, right: toluidine blue for thick section). Regrettably enough, this lethal condition may still be seen in Japan.



HTLV-1-associated myelopathy (HAM). The thoracic spinal cord is infiltrated by foamy macrophages around small vessels. The macrophages contain PAS-reactive granules. Demyelination is evident. The disease is endemic in Kyushu island, where incidence of adult T-cell leukemia/lymphoma is high. Left: H&E, right: LFB-PAS



Ossification of the yellow ligament. The degenerative change commonly occurs at the lower thoracic level and causes various types of compressive neurological symptoms. The disease is fairly common among the Japanese people. H&E



Paget's disease of the bone, a chronic metabolic bone disorder, causes increased bone resorption with activated osteoclasts and subsequent compensatory thickening of the bone. Bone deformities and fractures follow. It can be polyostotic or monoostotic, involving large bones. It is rare in Asia, including Japan.

Metabolic/hereditary disorders

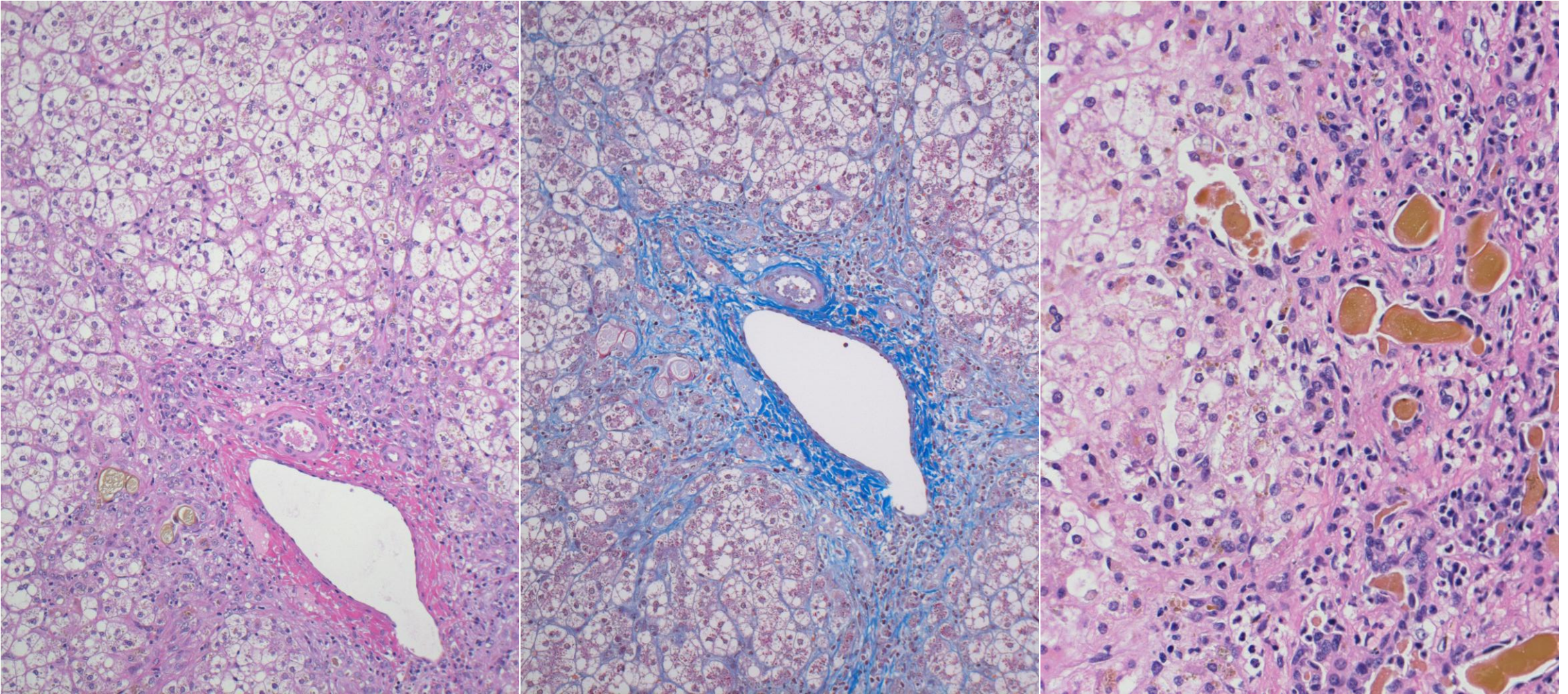
Cystic fibrosis is very rare in Japan.

Celiac disease is rare in Japan.

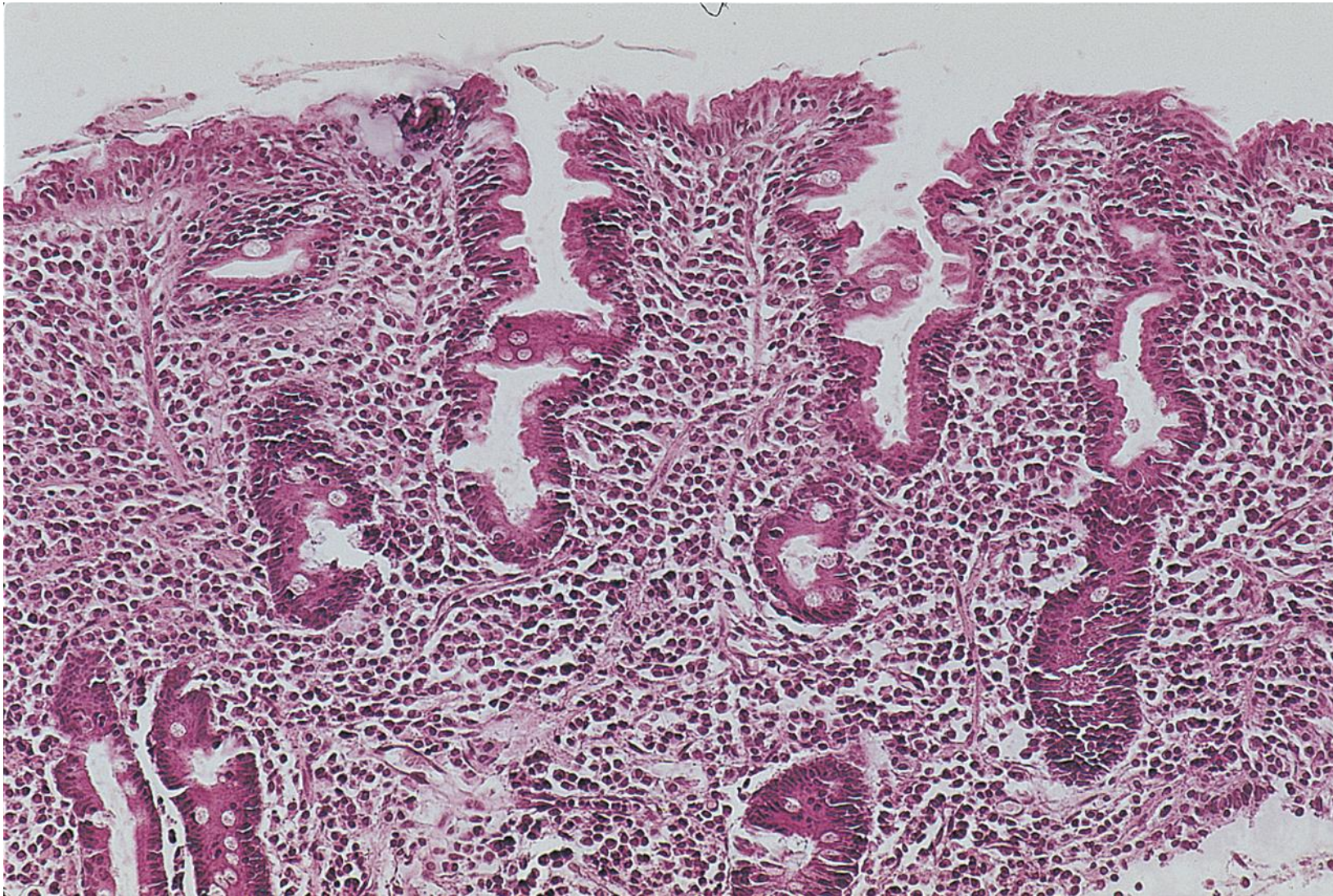
Werner syndrome is unique in Japan.

Color vision deficiency is relatively rare in Japan

Autosomal recessive hereditary disorders such as phenylketonuria are relatively rare in Japan.



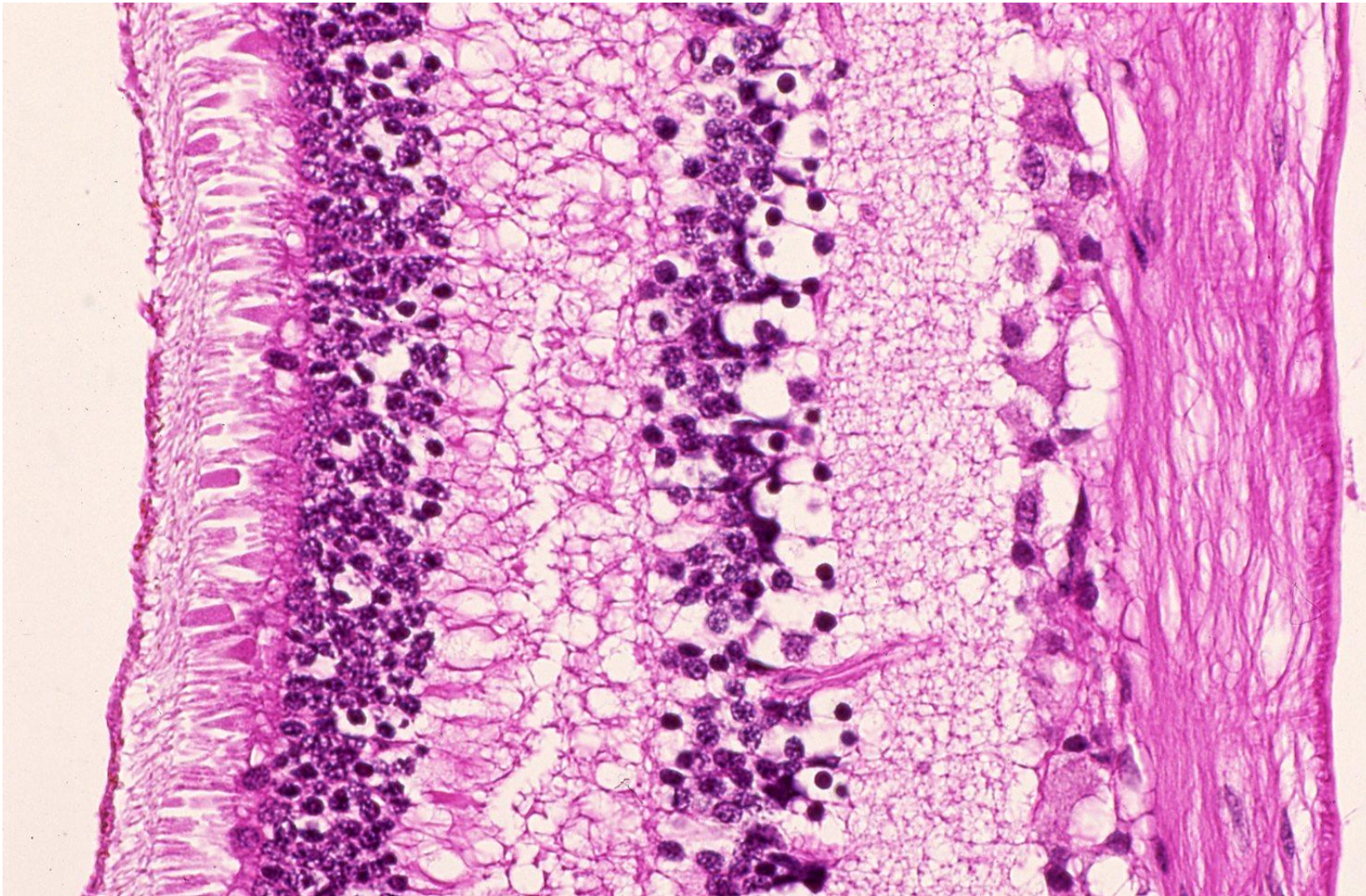
Cystic fibrosis, an autosomal recessive disorder, may involve the liver. In the liver of a 6 y-o boy, portal fibrosis and bile stasis are associated. The disease is very rare among the Japanese children. Left and right: H&E, center: Masson trichrome



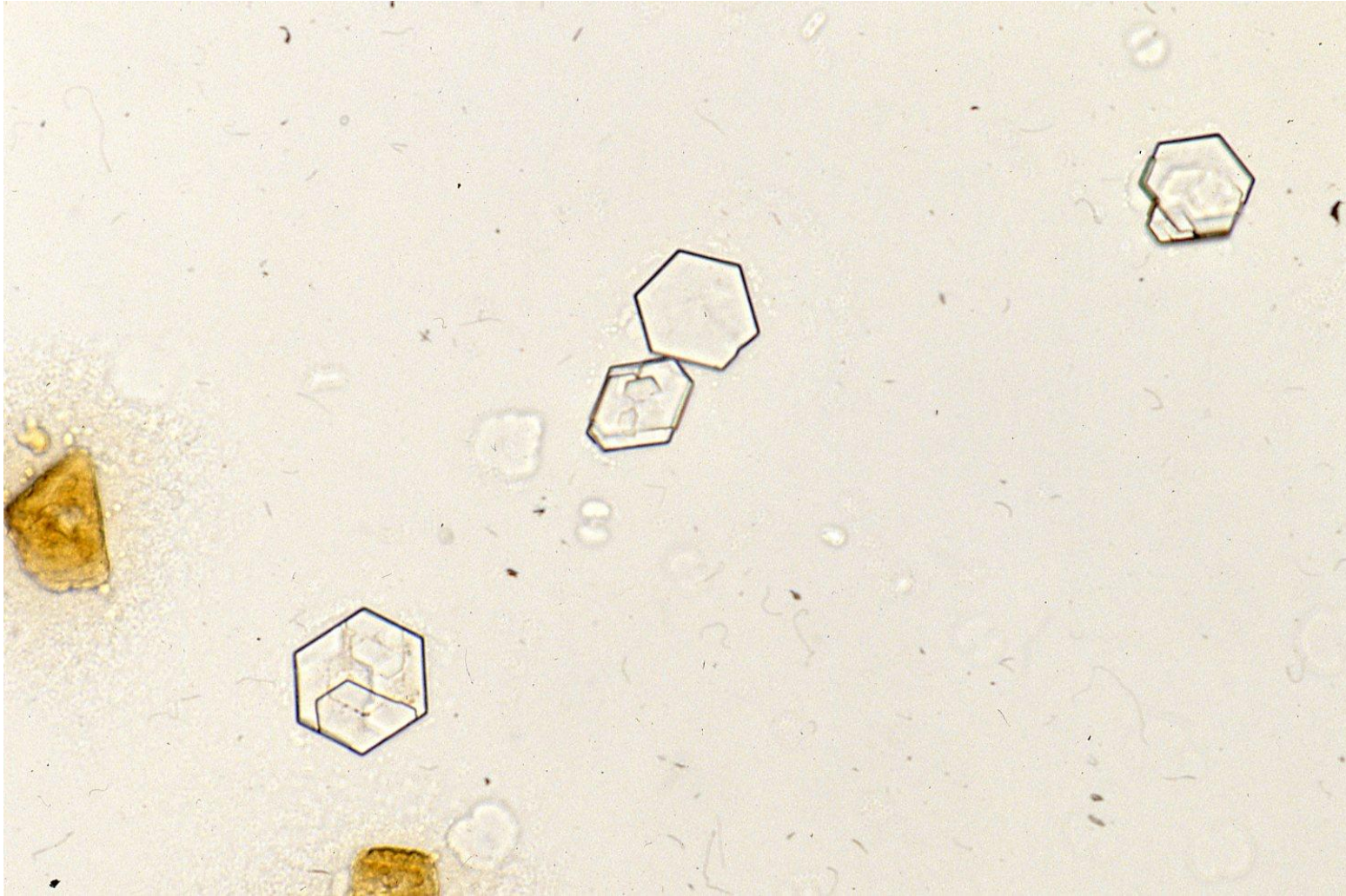
Celiac disease (celiac sprue or gluten-sensitive enteropathy) is an immune-mediated inflammatory disease of the small bowel, seen in genetically predisposed individuals. The chronically inflamed duodenum reveals villous atrophy and increase of intraepithelial lymphocytes. Celiac disease is very rare in Japan. H&E



Werner syndrome (adult progeria) in an autopsied 42 y-o male patient. Most cases of Werner syndrome have been reported from Japan. Skin atrophy, baldness (left) and advanced cataract (right: H&E) are noted. He died of systemic metastasis of malignancy of unknown origin.



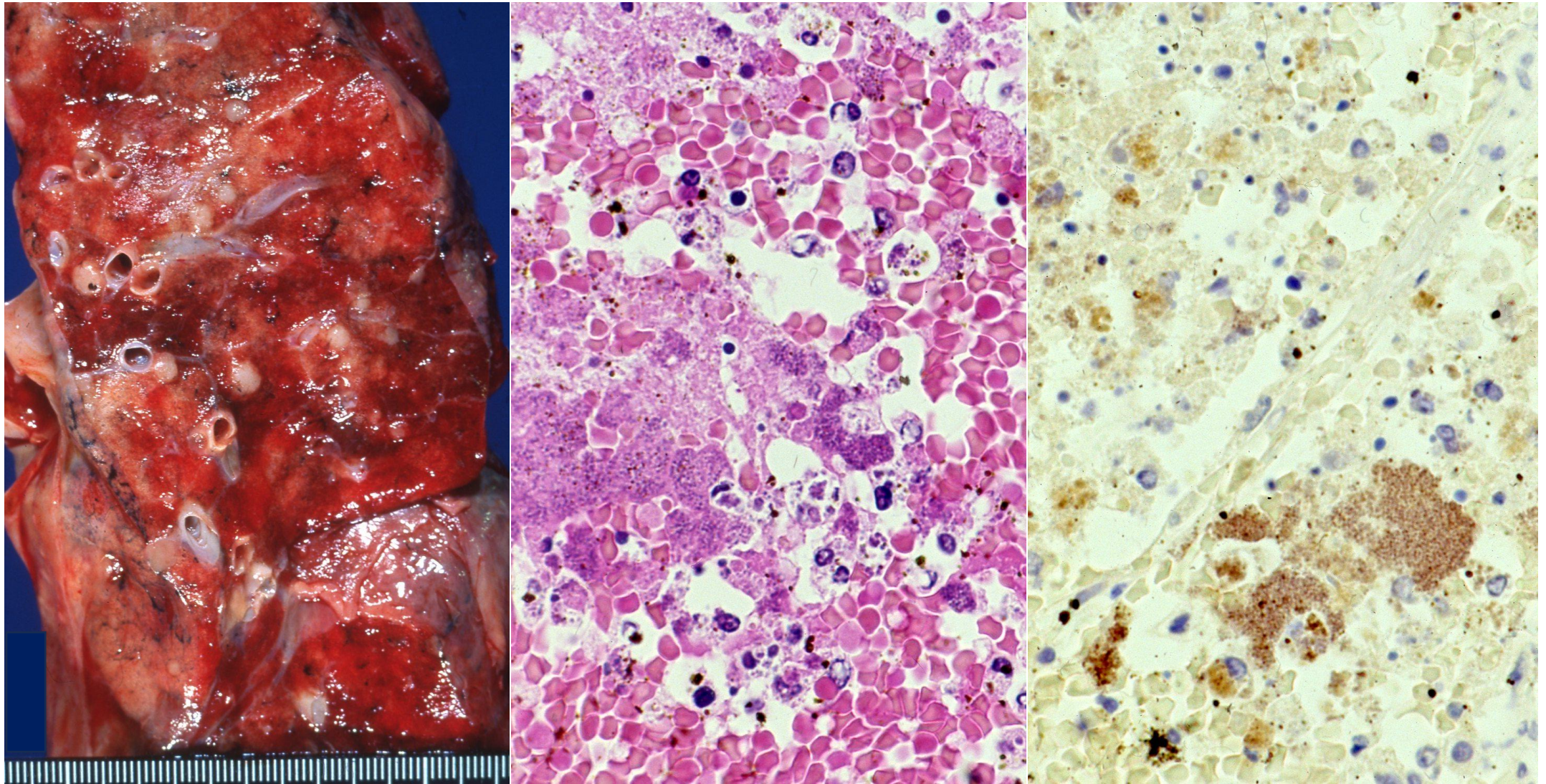
Normal retinal tissue (H&E). From left to right: photoreceptor layer (rods and cones), outer nuclear layer, outer plexiform layer, inner nuclear layer, inner plexiform layer, ganglion cell layer and nerve fiber layer. Color vision deficiency (color blindness) is caused by partial or complete lack of light-sensitive photoreceptors (cones). The incidence of color blindness in men is much lower in Japan than the western countries.



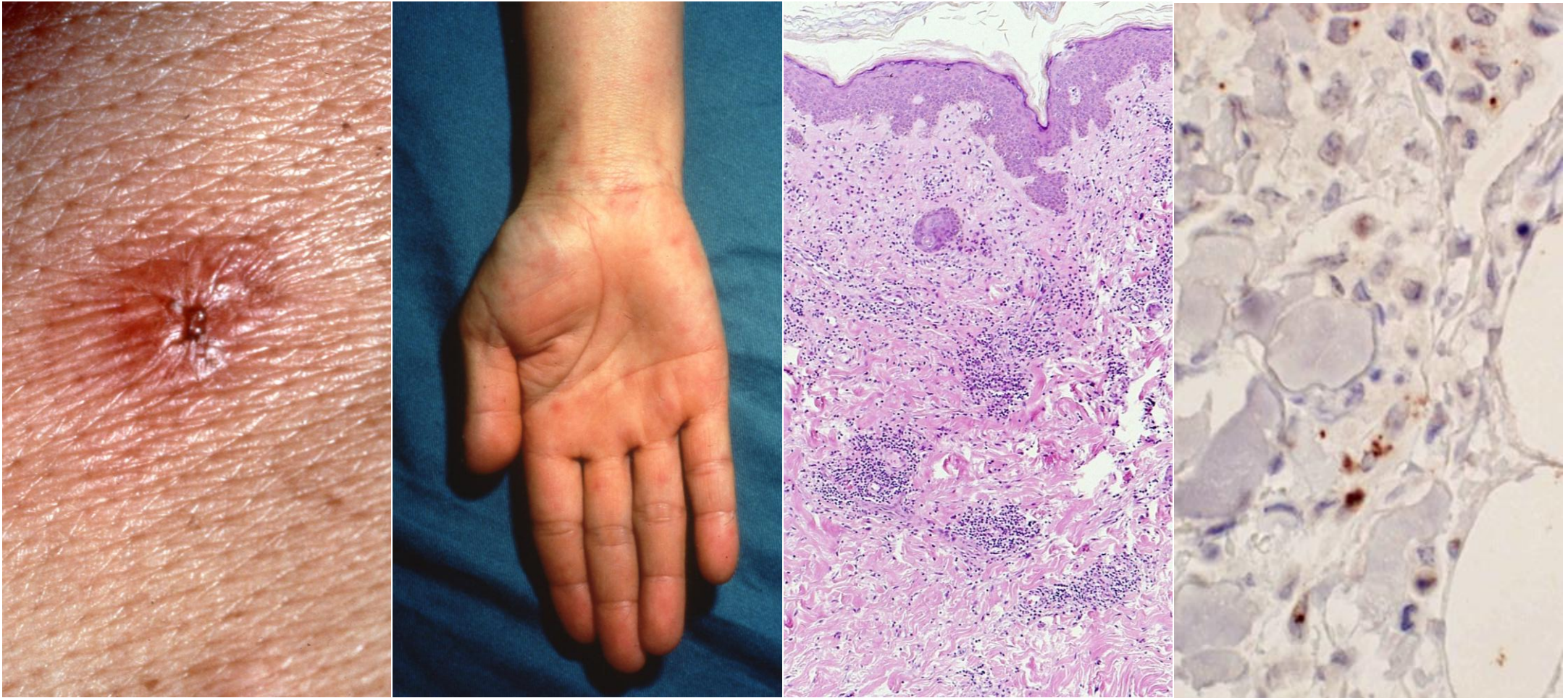
Urine sediment of cystinuria with an autosomal recessive trait. Translucent hexagonal-shaped cystine crystals are seen. In cystinuria, urinary stone makes the major symptom, while the intelligence level is retained. In phenylketonuria, excessive phenylalanine is excreted in the urine as a form of phenylketone. The phenylketone does not form crystals in the urine, and untreated infants show severe intellectual disability.

Infectious diseases

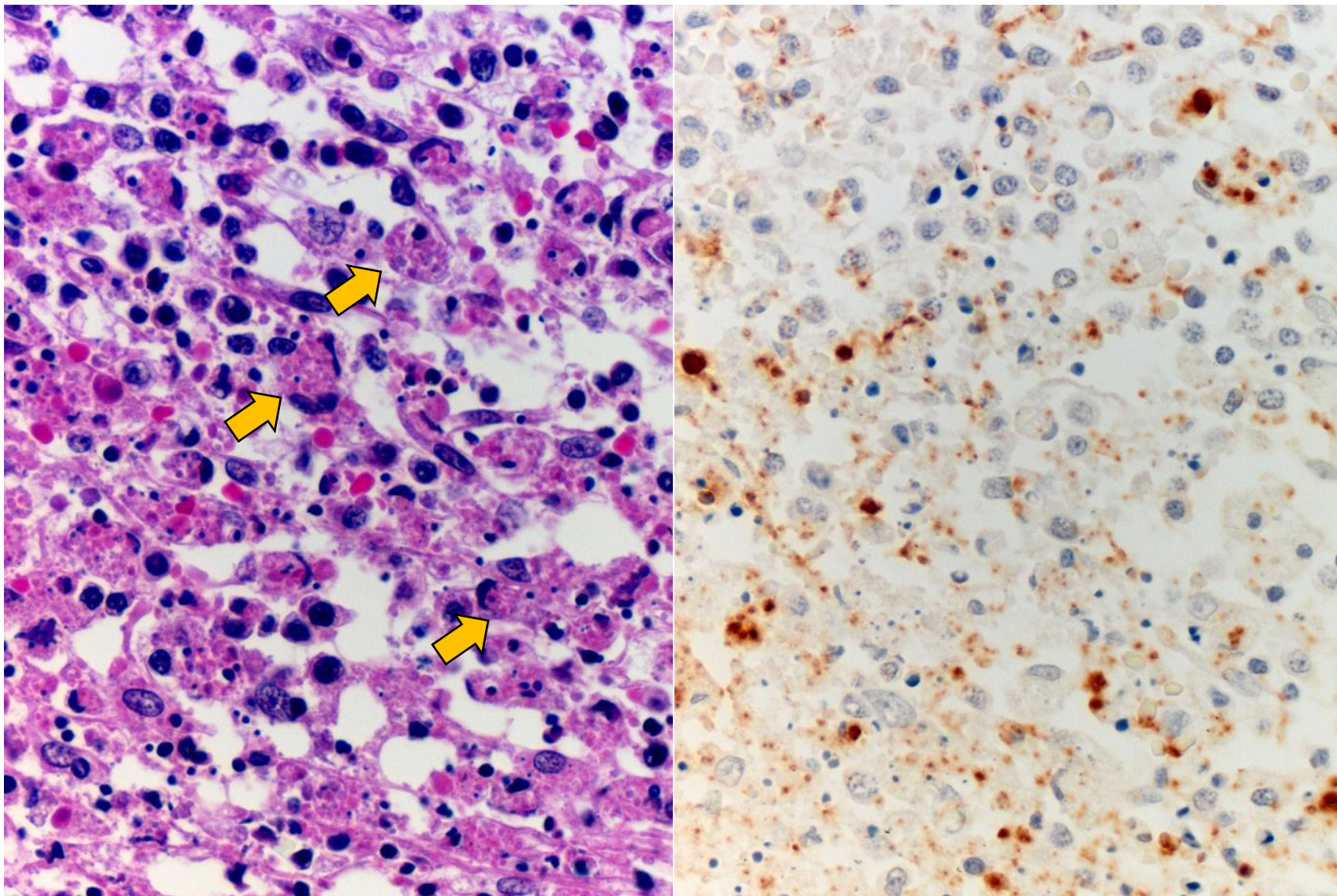
- High incidence of MRSA infection in Japan
- High incidence of Japanese spotted fever in Japan
- High incidence of severe fever thrombocytopenia syndrome (SFTS) in Japan
- High incidence of Japanese encephalitis in Japan (past history)
- High incidence of anisakiasis in Japan
- High incidence of creeping disease (cutaneous larva migrans) in Japan
- High incidence of sparganosis in Japan
- High incidence of Japanese schistosomiasis in Japan
- High incidence of metagonimiasis in Japan
- High incidence of cercarial dermatitis (paddy field dermatitis) in Japan
- High incidence of *Echinococcus multilocularis* infestation in Japan
- High incidence of *Diphyllobothrium nihonkaiense* infestation in Japan



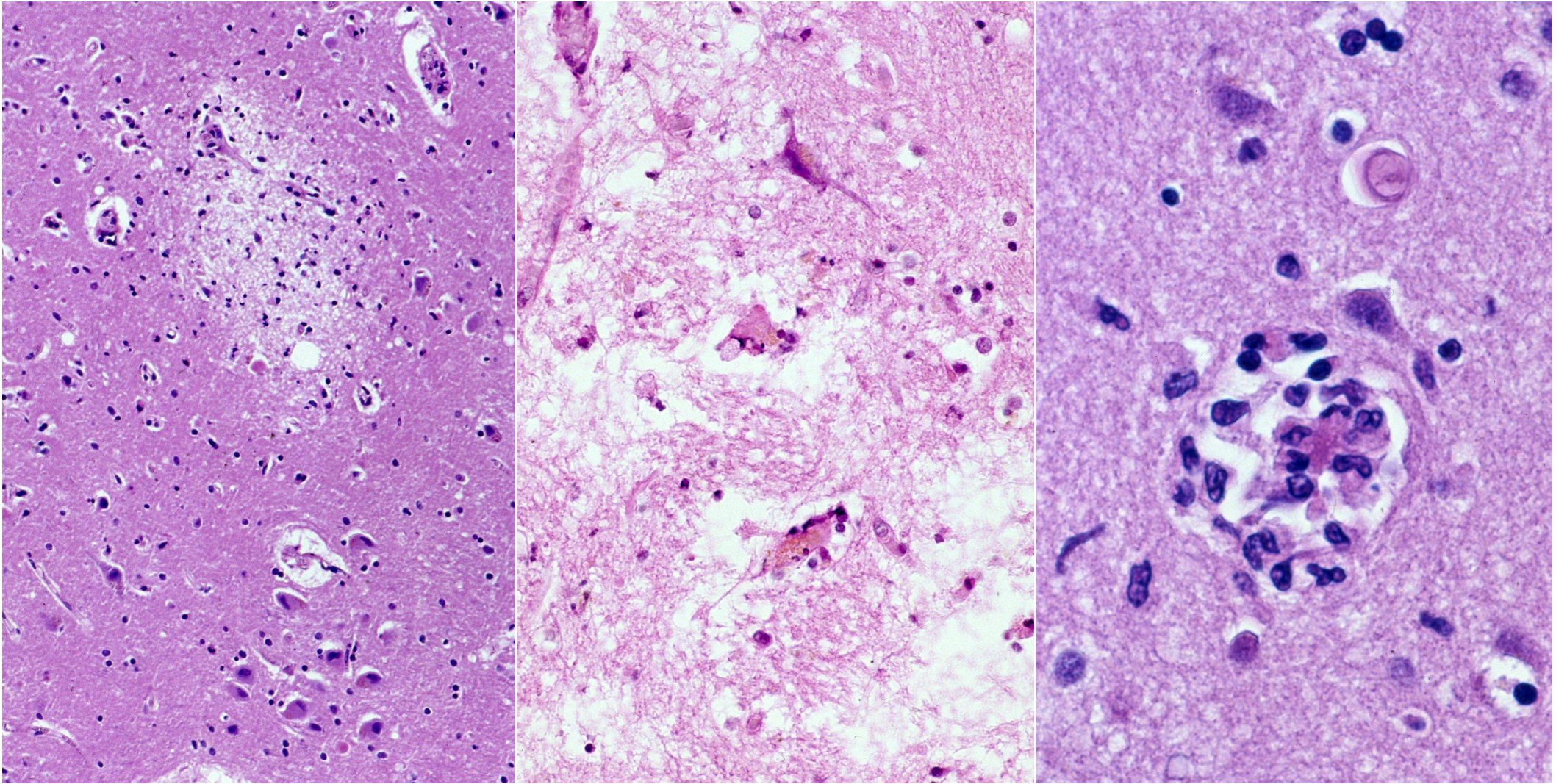
MRSA pneumonia seen in a 72 y-o male patient 3 months after esophagectomy for esophageal squamous cell carcinoma. The patient complicated septicemia to death. MRSA caused multifocal bronchopneumonia. The Gram-positive cocci are immunoreactive for penicillin-binding protein 2' (PBP2'). Left: macro at autopsy, center: H&E, right: immunostaining for PBP2'



Japanese spotted fever caused by *Rickettsia japonica*. The infection is mediated by the bite of a larval tick *Haemaphysalis longicornis*. The eschar and skin eruptions are shown. At the eschar, no tick can be identified. The dermis reveals perivascular infiltration of mononuclear cells. *R. japonica* antigen is demonstrated by a monoclonal antibody S3 in endothelial cells and macrophages. From the left to right: eschar, skin eruptions, H&E and immunostaining using Mab S3



The splenic lesion of severe fever thrombocytopenic syndrome (SFTS). In the red pulp, activated macrophages contain apoptotic bodies (arrows). *In situ* hybridization for the L segment of SFTS virus demonstrates the viral genome in the macrophages. Left: H&E, right: ISH for SFTSV



Japanese encephalitis is caused by the Japanese encephalitis virus (a type of Flavivirus, closely related to West Nile virus and St. Louis encephalitis virus) spread by Culex-type mosquitos. Pigs serve as a reservoir for the virus. Most infections result in little or no symptoms. Vaccines are effective to prevent the disease. In Japan, the disease has been eradicated, but is still endemic in southeastern Asian and pacific countries. Microscopically, focal clear-type necrosis (inflammatory edema) and neuronophagia are characteristic. H&E

No. Age/sex Diagnosis

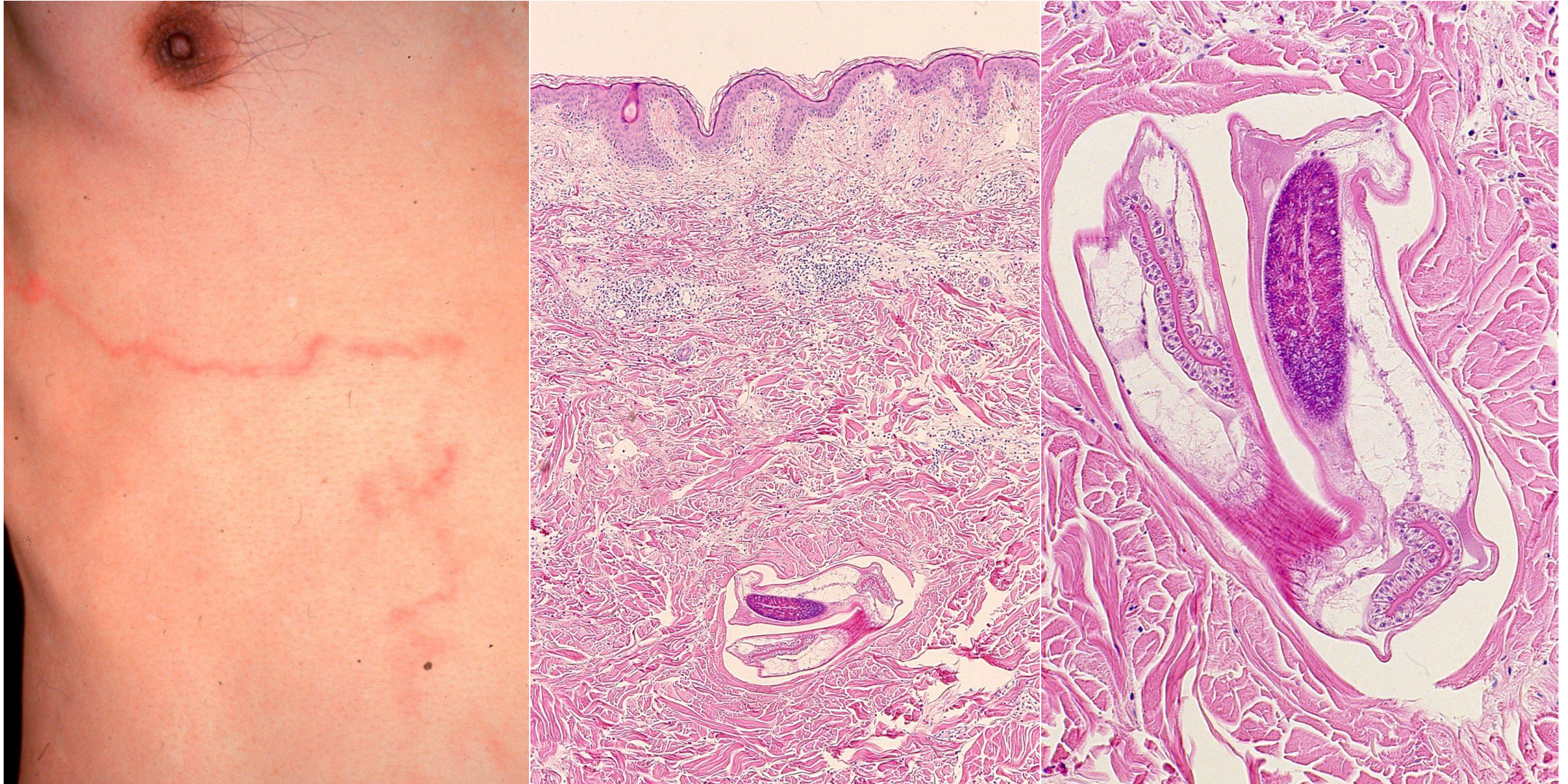
81	3	♂	Encephalitis
82	9	♂	Epidemische Meningitis
83	48	♂	Dementia paralytica
84	3年8月	♂	Encephalitis epidemica
85	1年	♀	meningitis etc.
86	31	♀	Encephalitis epidemica
87	40	♂	" 10 1/2
88	12年	♂	"
89	19	♀	" 19
90	5年6月	♂	"
91	1年10月	♀	"
92	2年4月	♂	"
93	19年11月	♀	Nierenkrebs
94	6	♀	Encephalitis epidemica
95	1年9月	♂	"
96	2年7月	♀	"
97	4年7月	♂	"
98	2年8月	♀	"
99	5年11月	♀	"
100	49	♂	"
101	2年6月	♀	"
102	4年1月	♂	"

Pathological autopsy record of the Department of Pathology, Keio University School of Medicine, Tokyo, Japan, in early 1960's

In the summer time of this endemic year in early 1960's, Japanese encephalitis (encephalitis epidemica) occupied most of the autopsy cases ($18/22 = 82\%$). 15 of 18 (83%) cases of Japanese encephalitis were young below 20 years. Of note is that only one of the 22 cases was kidney cancer (Nierenkrebs in German), and 21 of 22 autopsy cases (95%) belonged to infectious diseases, including epidemic meningitis, meningeal tuberculosis and dementia paralytica (neurosyphilis).



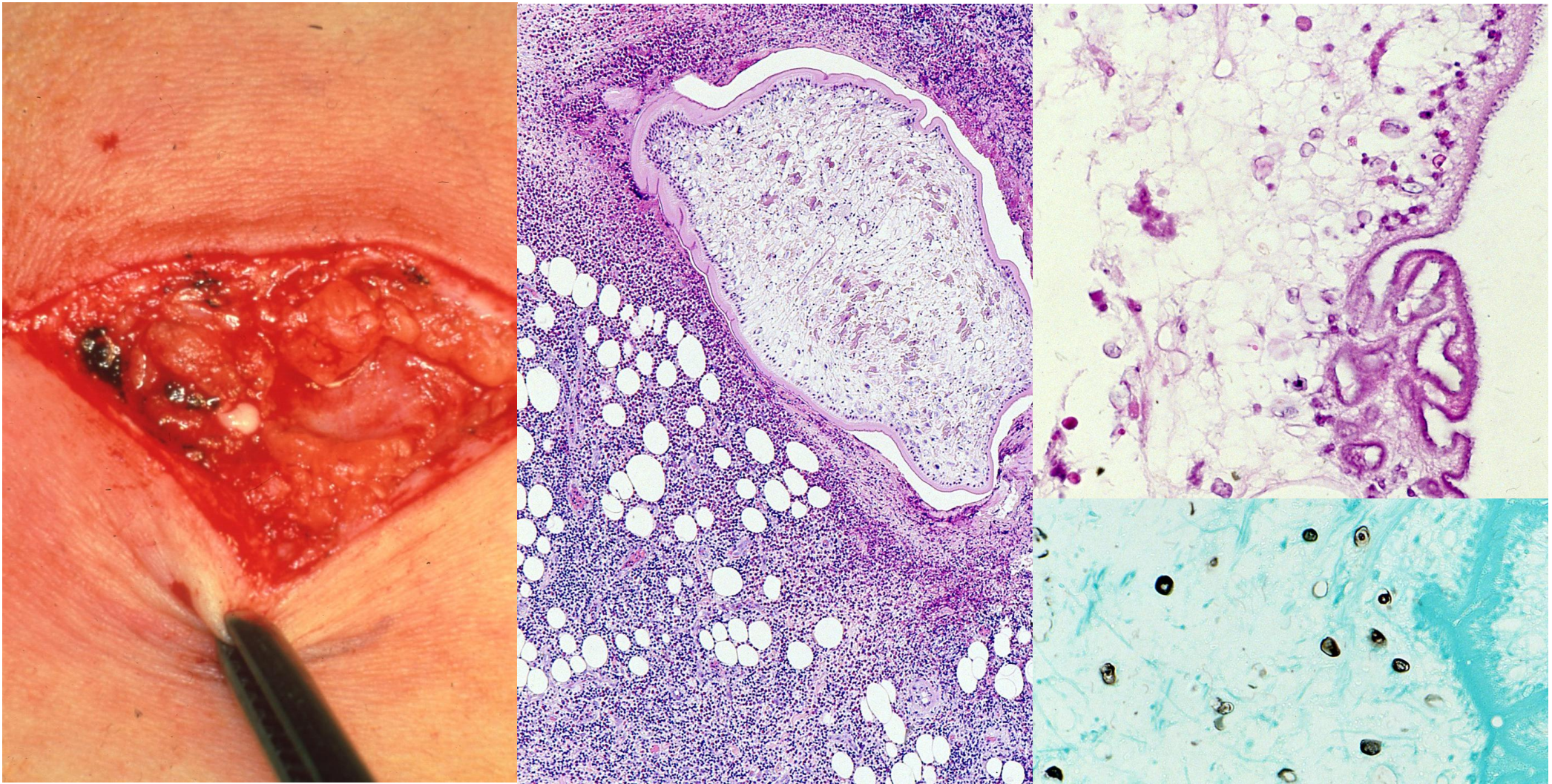
Intestinal anisakiasis. A cut surface of *Anisakis simplex* invading the small intestine. Eosinophilic reaction is evident. The nematode contains thick muscle layer beneath the cuticle, a pair of clover-shaped lateral chords, gut and Renette cells (an eosinophilic structure adjacent to the gut) are observed. H&E



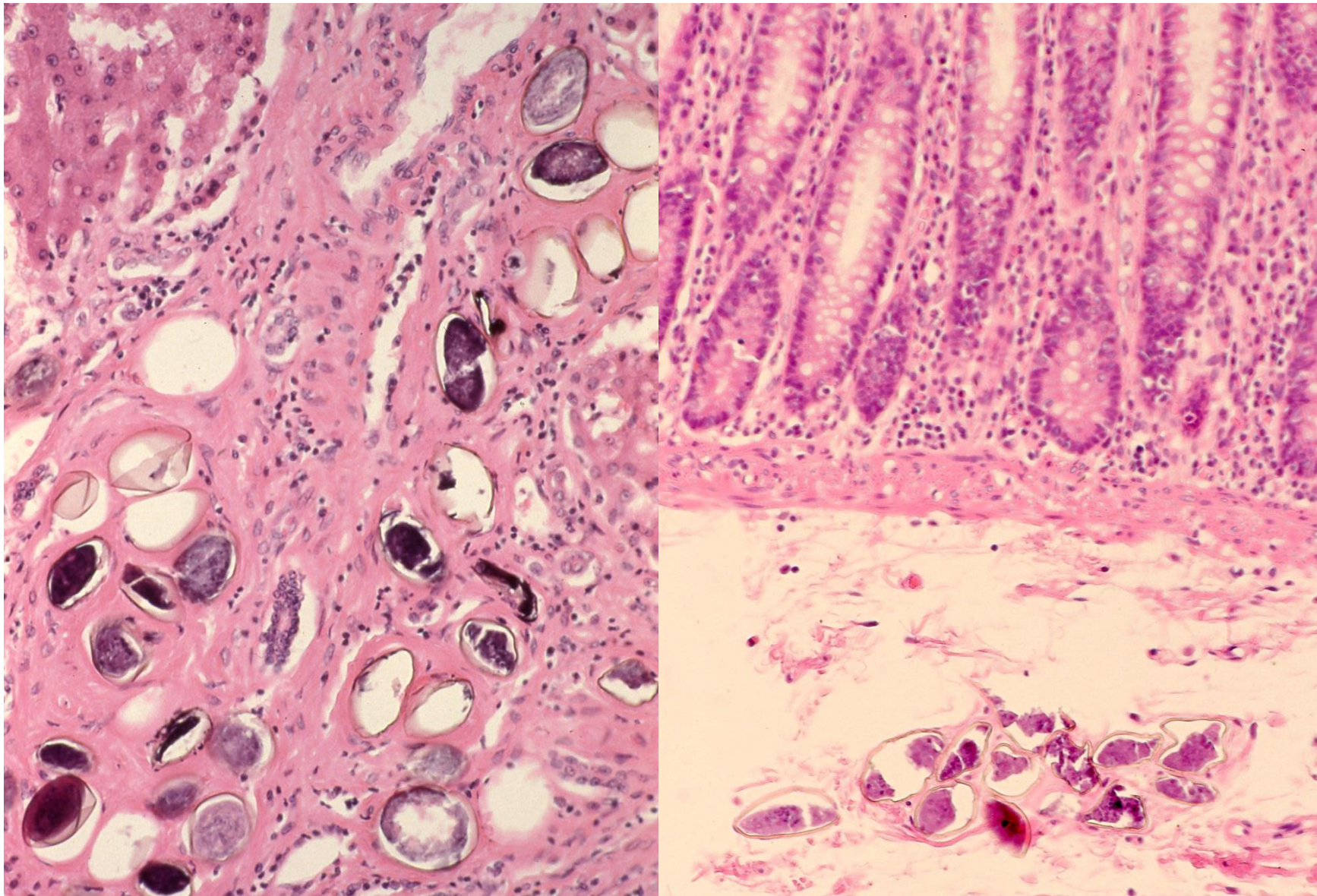
Gnathostomiasis presenting with creeping disease (cutaneous larva migrans). The nematode (*Gnathostoma*) larva results from ingestion of raw freshwater fish, including loach and Yamame (landlocked masu salmon). Cutaneous migration of spiruroid nematode larva is very unique in Japan, resulting from the intake of raw firefly squid, the seasonal product of Toyama Bay, Japan.



Spiruroid nematode larva infestation. In Japan, particularly in Toyama prefecture facing the Japan Sea, spiruroid type X larvae cause cutaneous creeping disease. The infestation is mediated by ingesting raw or undercooked firefly squid (*Watasenia scintillans*), a unique product of the Toyama Bay. The adult of the larva is *Crassicauda giliakiana* (baird's beaked whale: *Berardius bairdii*). Microscopically, a small-sized nematode, 6-10 mm in length and 0.1 mm in width, is seen in the dermis. Macro and H&E



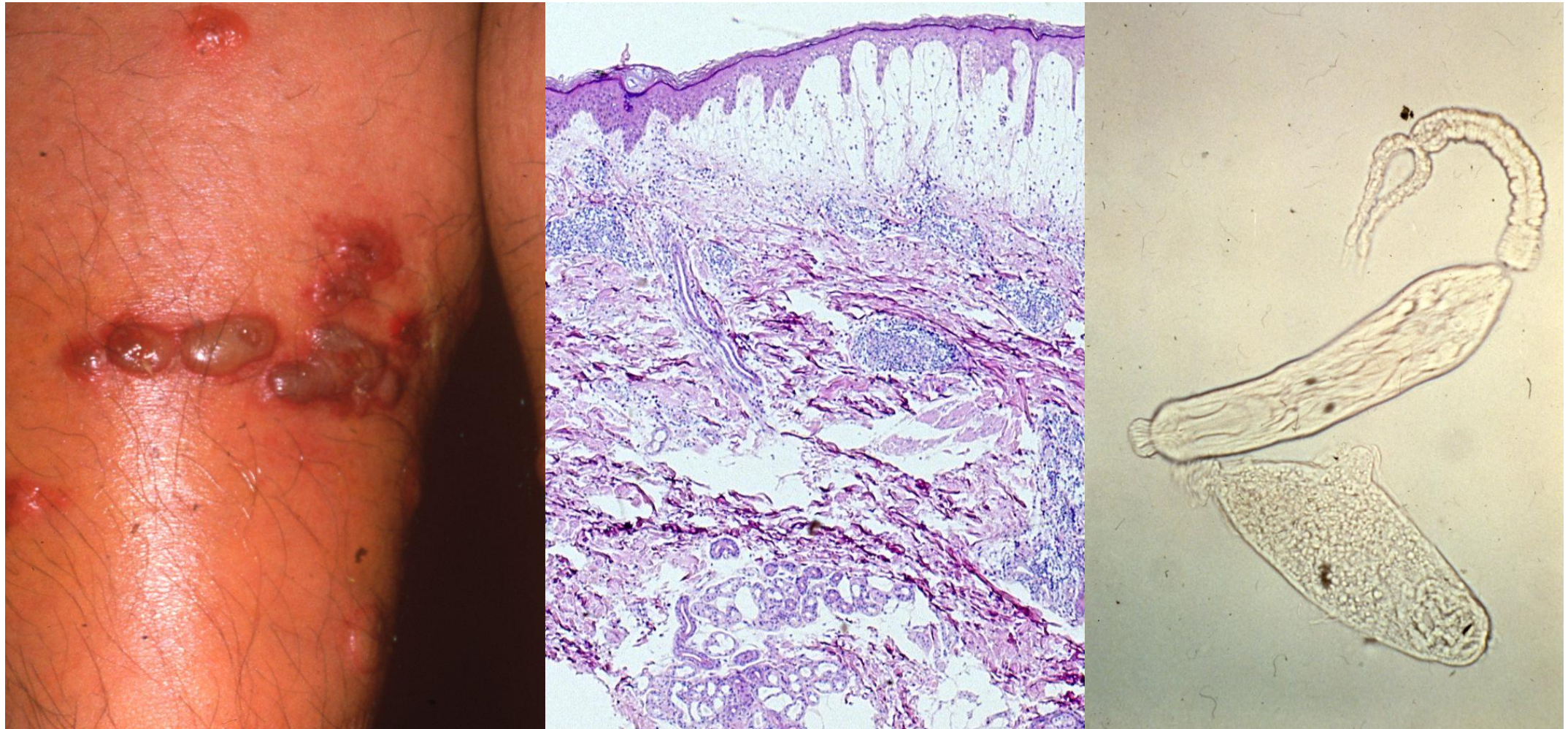
Sparganosis is a food-borne zoonosis caused by the plerocercoid larvae of the tapeworm, the genus *Spirometra*. The slowly creeping infestation, endemic east and southeast Asia including Japan, is acquired by ingesting the raw or undercooked meat of snakes or frogs, drinking pooled water containing copepods (the first intermediate host) or using raw flesh in traditional poultices. The Cestoda lacks the intestine. Microscopically, the presence of small round calcareous bodies (von Kossa-positive, right bottom) is characteristic of the Cestoda.



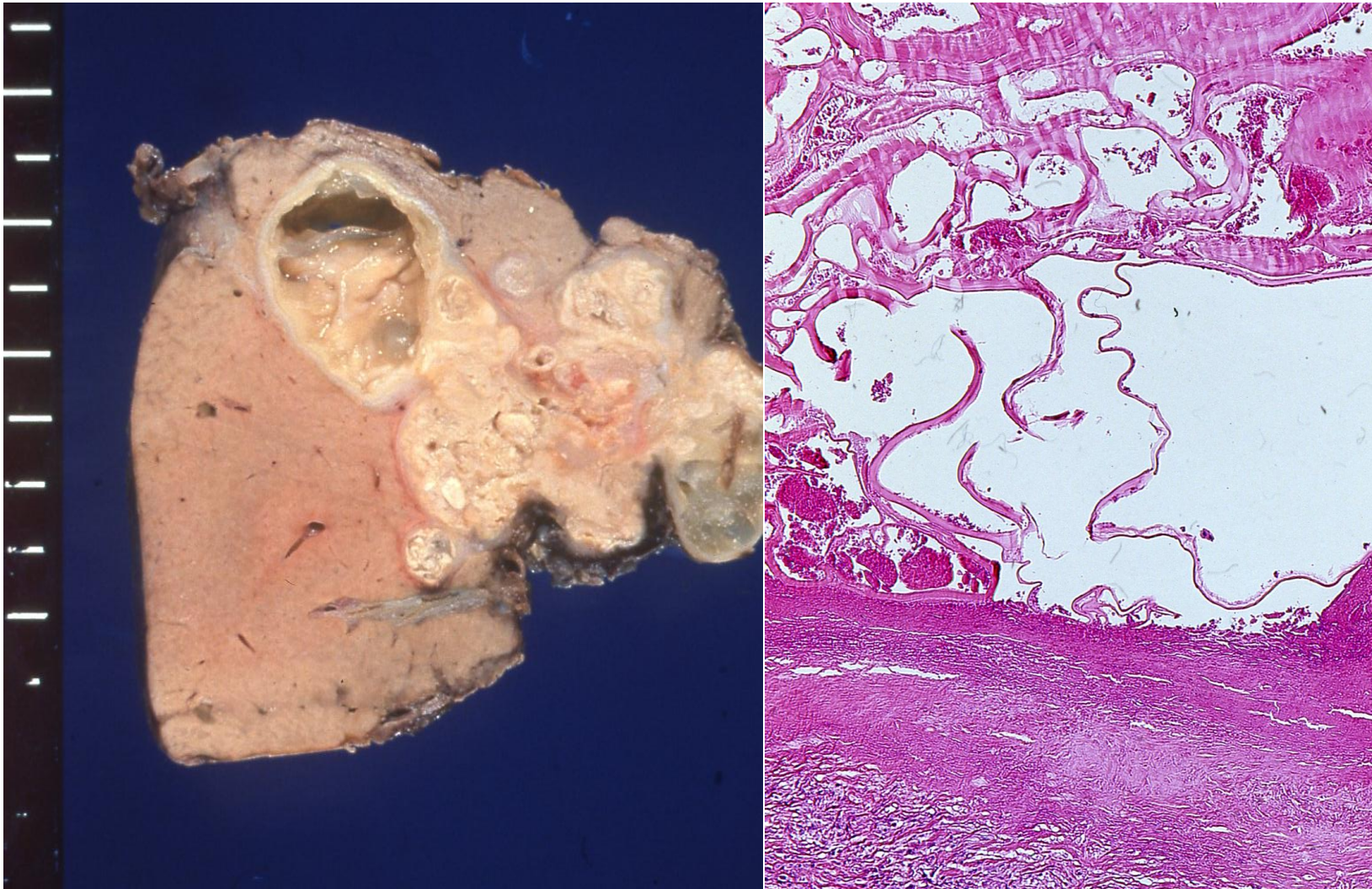
Japanese schistosomiasis. Calcified ova are seen in the portal triad of the liver and the submucosal layer of the colon. The aged patient lived in the endemic area for a long period of time. The disease was eradicated in Japan in 1976, but old ova may still be seen mainly in the liver and colon. H&E



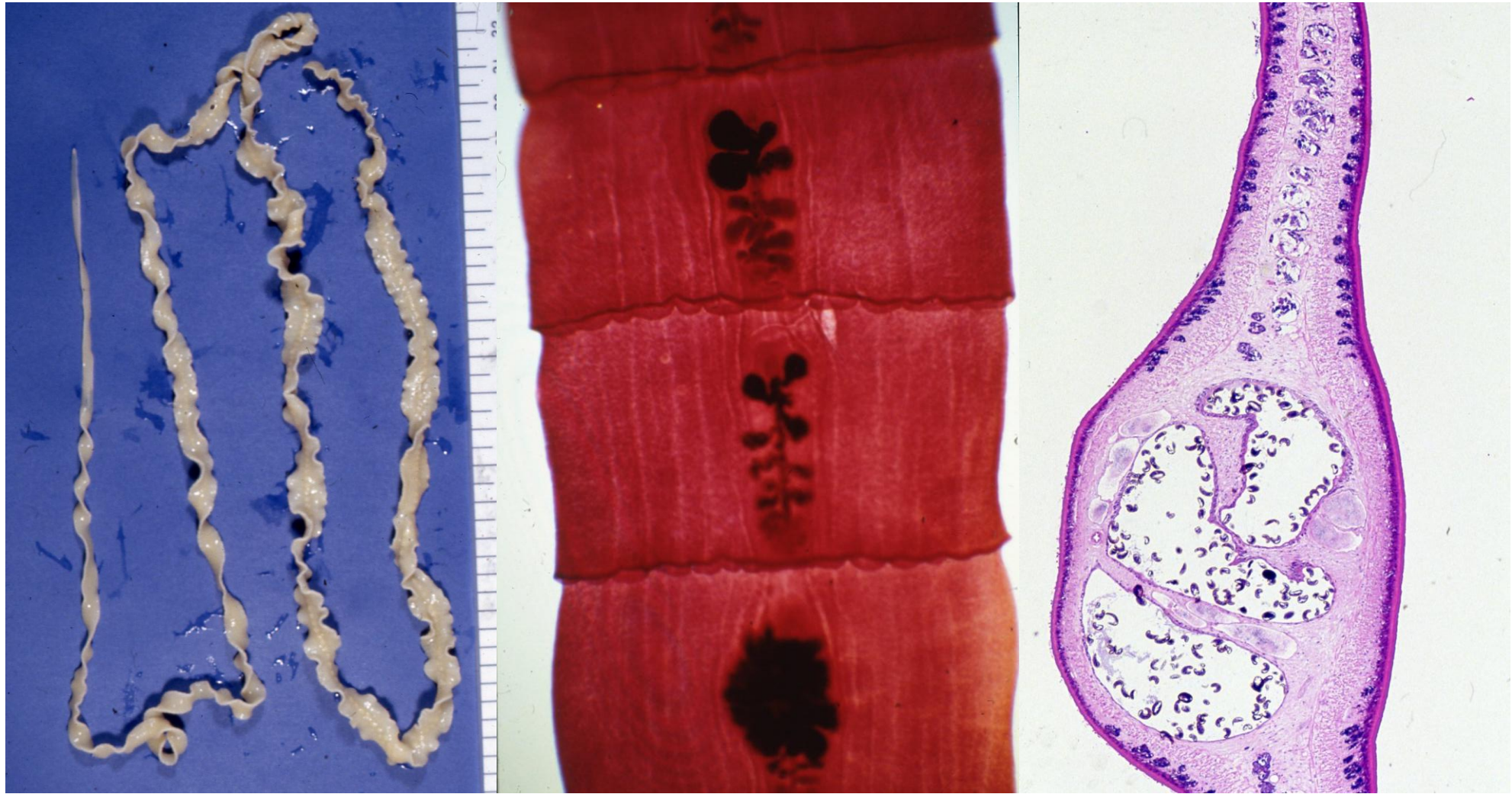
Metagonimus yokogawai. The ovum of *M. yokogawai* belongs to the smallest parasitic ovum found in the human feces (left). A mature adult of *M. yokogawai* infests the small intestinal mucosa (right: H&E). The infestation occurs as a result of gourmet diet of raw freshwater fish, such as the whitebait and sweetfish. The incidence of the infestation remains high in Japan at present.



Cercarial dermatitis (paddy field dermatitis or swimmer's itch) belongs to allergic contact dermatitis caused by cercaria of the water-borne bird schistosomes. It is commonly seen in the rice field workers in Japan who enter the water-filled rice field (paddy field) with naked legs. The leg skin at the water surface is affected to form blisters. Small water snails mediate the release of cercaria. Left: gross appearance of the leg, center: subepidermal blister (H&E) and right: a cercaria found in the water snail



Echinococcus multilocularis infestation is endemic in Hokkaido, the northernmost island in Japan. The liver with an invasive multicystic lesion was resected from a 41 y-o female patient. Protoscolex formation is not observed in the liver lesion. Left: macro (after formalin fixation), right: H&E



Diphyllobothrium nihonkaiense excreted from an elementary school girl. The cestode (tapeworm) consists of a chain of proglottids (body segments). No gut is noted in the body, and the cuticular villi absorb the nutrients. Both ovaries and testes are found (hermatroditism) (right: H&E). The infestation is mediated by ingestion of raw trout.